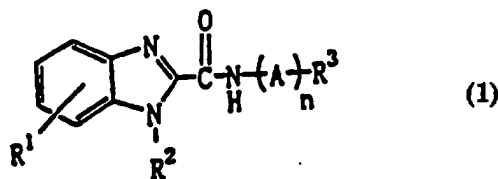




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
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| (51) International Patent Classification ⁶ : C07D 403/12, A61K 31/415, C07D 401/12, 521/00, 403/14, 401/14, 405/14 | | A1 | (11) International Publication Number: WO 97/03070 |
| | | | (43) International Publication Date: 30 January 1997 (30.01.97) |
| (21) International Application Number: PCT/JP96/01841 | | (74) Agents: ASAMURA, Kiyoshi et al.; New Ohtemachi Building, Room 331, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100 (JP). | |
| (22) International Filing Date: 3 July 1996 (03.07.96) | | | |
| (30) Priority Data: 7/171807 7 July 1995 (07.07.95) JP | | (81) Designated States: AU, CA, CN, KR, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). | |
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(54) Title: NOVEL BENZIMIDAZOLE DERIVATIVES HAVING CGMP-PHOSPHODISTERASE INHIBITING ACTIVITY



(57) Abstract

The present invention provides novel benzimidazole derivatives or salts thereof represented by general formula (1), wherein R¹ is a hydrogen atom or a halogen atom; R² is a phenyl-lower alkyl group; R³ is a heterocyclic group selected from the group consisting of an indolyl group, indoliny group, 1H-indazolyl group, 2(1H)-quinolinonyl group, 3,4-dihydro-2(1H)-quinolinonyl group and 1,4-benzoxazinyl group; A is a lower alkylene group; n is 0 or 1. The benzimidazole derivatives or salts of the present invention are effective agents for treating various arteriosclerotic diseases.

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DESCRIPTION

NOVEL BENZIMIDAZOLE DERIVATIVES HAVING CGMP-PHOSPHODISTERASE INHIBITING ACTIVITY

TECHNICAL FIELD

The present invention relates to novel benzimidazole derivatives and salts thereof.

BACKGROUND ART

- 5 Proliferation of the smooth muscle cells of the blood vessel induces hypertrophy of the intima of the blood vessel and, from a long-term view point, it causes, arteriosclelerotic diseases such as myocardial infarction, cerebral infarction and the like.
- 10 Moreover, from a short-term view point, it induces reobstruction of the blood vessel after treatments of percutaneous transluminal coronary angioplasty (PTCA), stent and/or aterectomy. In consideration of the present situation, the therapeutic effects of conven-
- 15 tional medicines used therefor are thought of as within certain limits, because they are classified as agents of indirectly effective for curing the diseases induced by the promotion factors of hypertrophy of the interim, for example hyperlipidemia, hypertension and the like.
- 20 Therefore, development of essentially effective medicines therefor have been eagerly expected.

Generally, it is known that proliferation of

the smooth muscle cells is related to the influence of cyclic guanosine 3',5'-monophosphate (cGMP). In this connection, pharmaceutical preparations of nitro group-containing compound known as coronary vasodilators
5 activate the enzymatic activity of guanylate cyclase, and accentuate the production of cGMP, and also inhibit the proliferation of the cells. However, the pharmaceutical preparations of nitro group-containing compound are scarcely used for treatment of arterio-
10 sclerotic diseases which need to be administered for a long period of time, because the effect of the pharmaceutical preparations of nitro group-containing compound can be sustained only for a quite short time, and when they are administered repeatedly, then the
15 tolerance against said pharmaceutical preparations may be occurred. On the other hand, in recent years, there have been reported several pharmaceutical preparations which can increase the concentration of cGMP by inhibiting the enzymatic activity of the enzyme [i.e.,
20 cGMP-PDE (cGMP-phosphodiesterase)] for decomposition of cGMP. However, there have not been suggested the activity for inhibiting proliferation of the smooth muscle cells performed by pharmaceutical preparations. The guanine derivative which was reported recently in
25 an academic conference (IBC's International Conference on RESTENOSIS, 1994, U. S. A.) is the only known compound having both effects for inhibiting the enzymatic activity of cGMP-PDE and for inhibiting proliferation

of the smooth muscle cells.

In consideration of the present status of such pharmacotherapy, and referring to the fact that cGMP relates to proliferation of the smooth muscle cells of the blood vessel, the present inventors have made an extensive research work regarding pharmaceutical preparations having the activity for inhibiting proliferation of the smooth muscle cells of the blood vessel which acts directly to the cells thereof, and can be used as the essential agent for treating arteriosclerotic diseases.

As the results, the present inventors have found the fact that the objective compounds, having the activity for inhibiting proliferation of the smooth muscle cells of the blood vessel, are existed among benzimidazole derivatives having property for inhibiting the enzymatic activity of cGMP PDE, thus the present invention has been completed.

Related art references which disclose compounds having chemical structural formulas similar to those disclose in the present invention are JP-A-2-306916, U.S. Patent No. 4,886,803, U.S. Patent 4,551,421, JP-A-62-246546, JP-A-4-346974, JP-A-61-167952, U.S. Patent No. 4,994,477, U.S. Patent No. 5,098,924, EP-A1-0560407, EP-A1-0407217, JP-A-64-65551, JP-A-1-96645, and JP-A-7-133224, however, those references neither disclose nor suggest benzimidazole derivatives of the present invention, and do not touch

on inhibition of the enzymatic activity of cGMP PDE at all which benzimidazole derivatives of the present invention possess.

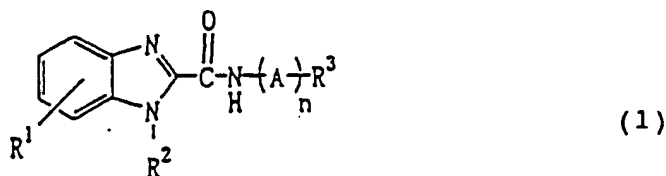
Furthermore, references JP-A-5-222000, WO-A-93-07124, and WO-A-94-22855 disclose structural similar compounds having inhibition of the enzymatic activity of cGMP PDE, however, those references neither disclose nor suggest benzimidazole derivatives of the present invention.

10

DISCLOSURE OF THE INVENTION

Benzimidazole derivatives of the present invention are novel compounds which have not been reported in any literature, and are represented by the general formula (1) as follows:

15



[wherein R¹ is a hydrogen atom or a halogen atom;

R² is a phenyl-lower alkyl group;

R³ is a heterocyclic group selected from the group consisting of an indolyl group, indolinyl group, 1H-indazolyl group, 2(1H)-quinolinonyl group, 3,4-dihydro-2(1H)-quinolinonyl group and 3,4-dihydro-1,4(2H)-benzoxazinyl group, said heterocyclic group may

20

have 1 to 3 substituents selected from the group consisting of: a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridylcarbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group));

a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower

alkyl group;

A is a lower alkylene group; and

n is 0 or 1.].

The benzimidazole derivatives of the present
5 invention possess weak activity for inhibiting the
enzymatic action of cAMP PDE, while they possess strong
activity for inhibiting the enzymatic action selec-
tively against cGMP PDE.

The benzimidazole derivatives of the present
10 invention possess activity for inhibiting proliferation
of the smooth muscle cells, especially they possess
strong activity for inhibiting proliferation of the
mesenchymal cells. The activity for inhibiting proli-
feration of the smooth muscle cells was determination
15 by measuring the activity for inhibiting proliferation
of rat A10 cell (in vitro), and confirmed. The rat
A10 cell is a cell strain derived from smooth muscle
of rat embryo thoracic aorta, and the biological
property thereof is described in Exptl. Cell Res.
20 Vol. 98, (1976), pages 349-365, (B. W. Kimes and B. L.
Brandt). The activity for inhibiting proliferation
of the fibroblasts and mesangial cells were determined
by measuring the activity for inhibiting proliferation
of human fibroblasts or rat mesangial cells in place of
25 rat A10 cell, by the procedure similar to that of
described in the same literature, and confirmed strong
activities for inhibition. The activity for inhibiting
proliferating of T-cells was determined by procedure of

the experiment as described in "Current Protocol in Immunology" Chapter 3, page 12 [compiled by Coligan, et al., (1991), (published by Willy Interscience)], and confirmed. As mentioned above, the benzimidazole derivatives of the present invention also possess immunosuppressive activity based on the activity for inhibiting proliferation of T-cells.

The benzimidazole derivatives of the present invention possess activity for inhibiting synthesis and secretion of collagen. Thus, the activity was confirmed by culturing human fibroblast and by method as described in Clin. Invest., Vol. 83, (1989), pages 1160-1167 (K. Mackay, et al.) and by applying assay method as described in Calcif. Tissue Int., Vol. 35, (1983), pages 542-548 (M. Kumegawa, et al.).

Furthermore, the benzimidazole derivatives of the present invention also possess antiinflammatory activity. In case of using as a drug for external use, the antiinflammatory activity of benzimidazole derivative was confirmed by the procedures of experiment as described in Agents Actions, Vol. 26, (1989), page 319 (Carlson, et al.) [Test animals and administration method were partly revised]. Said inflammatory activity of benzimidazole derivative of the present invention was confirmed in detail as described in (6) Determination of the activity for inhibiting TPA-induced inflammation as described later in this specification.

Proliferation of the smooth muscle cells of the blood vessel is the major cause of arteriosclerosis. [Nature Vol. 362, (1993), pages 801-809 (Russell Ross)]. Moreover, proliferation of fibroblast and synthesis and secretion of collagen are also the causes of arteriosclerosis. [Am. J. Pathol., Vol. 125, (1986), pages 191-207 (A. M. Gown, et al.)]. In the case of diabetes mellitus, the smooth muscle cells show tendency of abnormal proliferation. [Eu. J. Clin. Invest. Vol. 23, (1993), pages 84-90 (M. Kawano, et al.)]. Proliferation of fibroblast as well as synthesis and secretion of collagen induce pulmonary fibrosis. [Am. Rev. Respir. Dis., Vol 138, (1988), pages 703-708 (G. Raghu, et al.); and CHIRYOU-GAKU (Therapeutics), Vol. 28, (1994), pages 62-66, (Toshihiko Sakai, et al.)]. Inhibition of the enzymatic activity of cGMP PDE inhibits aggregation of platelets, as well as effective for prevention and treatment of allergy, asthma, psoriasis and formation of thrombus. [Trends Pharmacol. Sci., Vol. 12, (1991), pages 19-27 (C. D. Nicholson, et al.)]. Increase of the amount of cGMP lowers blood pressure. [Circ. Res., Vol. 74, (1994), pages 416-421 (A. Koller, et al.) and DOHMYAKU KOUKA NO BUNSHI IGAKU (Molecular Medicine of Arteriosclerosis) (compiled by Tohru Kita, 1994, published by YOHDO-SHA, pages 27-28 and 147-164)].

As explained above, according to the pharmacological activities performed by the benzimidazole

derivatives of the present invention, they can be applied to prevention and treatment of various diseases for example, diseases related to cGMP, diseases induced by proliferation of the smooth muscle cells and
5 fibroblast, diseases related to synthesis and secretion of collagen, and they can be further applied to prevention and treatment of skin diseases relating to immune and inflammation. As to these diseases, there can be exemplified, reobstruction of the blood vessel
10 occurred after the treatments of PTCA, anginoplasmy and operation of bypass, arteriosclerotic diseases [e.g., angina pectoris, myocardial infarction, cerebral infarction, cerebrovascular dementia, transient ischemic attack (TIA), disfunction of peripheral
15 circulation, complication of diabetes mellitus, atherosclerosis, arteriolosclerosis, fibrous hypertrophy of artery and the like], cell proliferative diseases other than arteriosclerotic diseases (e.g., renal disease, asthma, bronchitis, proliferative
20 dermatitis, keloidosis, hyperplastic scar, glaucoma and the like), pulmonary fibrosis, collagen disease, psoriasis, allergic diseases (especially, atopic dermatitis and chronic contactive dermatitis), other dermatitises, hypertension, organopathy induced by
25 hypertension, cardiac failure, hypercardia and the like.

The benzimidazole derivatives of the present invention can be administered orally and non-orally by

making them as in the form of suitable pharmaceutical preparations, and in case of apply to dermatic diseases, a pharmaceutical preparation made for external use can be applied by coating directly onto the diseased part. The effectiveness of the benzimidazole derivatives of the present invention applied in the form of pharmaceutical preparations for external use was confirmed by conducting experiments as described in J. Dermtol. Sci., Vol. 8, (1994), page 54 (Kitagaki, et al.) and Agents Actions, Vol. 26, (1989), page 319 (Carlson, et al.). [Animal test and method of administration were partly revided.] Detailed explanation relating to activity for inhibiting TPA-induced edema will be disclosed in Pharmacological Test (6), as mentioned later in this specification. Models in Dermatology, Vol. 1, pages 50-58 [(compiled by H. I. Maibach, N. J. Lowe) (published by Krager, Basel) 1985] describes that the experiment as described in the latter literature (Agents Actions by Carlson, et al.) is a model of psoriasis.

As can be seen from the result of experiment conducted by using rat carotid paratripsis model [Am. J. Pathol., Vol. 141, (1992), pages 685-690 (U. Zeymer, et al.)] the benzimidazole derivatives of the present invention are effective not only in vitro test but also in vivo test.

In case of oral administration, the benzimidazole derivatives of the present invention can be

attained to keep blood concentration sufficient to
manifestation of pharmacological effect, and the number
of oral administration per day can be set as small
number, because the duration of blood concentration and
5 action time thereof can be kept for quite long time.

The benzimidazole derivatives of the present
invention are characterized by having quite weak
activity of acute vasodepression effect, systolic
potentiation effect and cardiac rate increasing effect
10 at the dosage of showing inhibitory effect of cGMP PDE,
and at the dosage of showing inhibitory effect of
proliferation of the smooth muscle cells.

The benzimidazole derivatives of the present
invention do not show strong toxicity even though they
15 are administered for short-term or administered
continuously for long-term.

As to the benzimidazole derivatives of the
present invention represented by the general formula
(1), there are various types of derivatives are
20 included as follows:

① Benzimidazol derivatives or salts thereof
represented by the general formula (1), wherein R^1 is a
hydrogen atom; R^2 is the same as defined in the general
formula (1) as mentioned above; n is 0, and R^3 is an
25 indolyl group (wherein the substituents of the indolyl
group are the same as defined in the general formula
(1) as mentioned above).

② Benzimidazol derivatives or salts thereof

represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is an indoliny group (wherein the substituents of the indoliny group are the same as defined in the general formula (1) as mentioned above).

③ Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is a 1H-indazolyl group (wherein the substituents of the 1H-indazolyl group are the same as defined in the general formula (1) as mentioned above).

④ Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is 2(1H)-quinolinonyl group (wherein the substituents of the 2(1H)-quinolinonyl group are the same as defined in the general formula (1) as mentioned above).

⑤ Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is 3,4-dihydro-2(1H)-quinolinonyl group (wherein the substituents of the 3,4-dihydro-2(1H)-quinolinonyl group are the same as defined in the general formula (1) as mentioned above).

(6) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is
5 3,4-dihydro-1,4(2H)-benzoxazinyl group (wherein the substituents of the 3,4-dihydro-1,4(2H)-benzoxazinyl group are the same as defined in the general formula (1) as mentioned above).

(7) Benzimidazol derivatives or salts thereof
10 represented by the general formula (1), wherein R^1 is a halogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is an indolyl group (wherein the substituents of the indolyl group are the same as defined in the general formula
15 (1) as mentioned above).

(8) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a halogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is an
20 indolinyl group (wherein the substituents of the indolinyl group are the same as defined in the general formula (1) as mentioned above).

(9) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a
25 halogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 0, and R^3 is a 1H-indazolyl group (wherein the substituents of the 1H-indazolyl group are the same as defined in the

general formula (1) as mentioned above).

(10) Benzimidazol derivatives or salts
thereof represented by the general formula (1), wherein
 R^1 is a halogen atom; R^2 is the same as defined in the
5 general formula (1) as mentioned above; n is 0, and R^3
is a 2(1H)-quinolinonyl group (wherein the substituents
of the 2(1H)-quinolinonyl group are the same as defined
in the general formula (1) as mentioned above).

(11) Benzimidazol derivatives or salts
10 thereof represented by the general formula (1), wherein
 R^1 is a halogen atom; R^2 is the same as defined in the
general formula (1) as mentioned above; n is 0, and R^3
is a 3,4-dihydro-2(1H)-quinolinonyl group (wherein the
substituents of the 3,4-dihydro-2(1H)-quinolinonyl
15 group are the same as defined in the general formula
(1) as mentioned above).

(12) Benzimidazol derivatives or salts
thereof represented by the general formula (1), wherein
 R^1 is a halogen atom; R^2 is the same as defined in the
20 general formula (1) as mentioned above; n is 0, and R^3
is a 3,4-dihydro-1,4(2H)-benzoxazinyl group (wherein
the substituents of the 3,4-dihydro-1,4(2H)-
benzoxazinyl group are the same as defined in the
general formula (1) as mentioned above).

25 (13) Benzimidazol derivatives or salts
thereof represented by the general formula (1), wherein
 R^1 is a hydrogen atom; R^2 is the same as defined in the
general formula (1) as mentioned above; n is 1, and R^3

is an indolyl group (wherein the substituents of the indolyl group are the same as defined in the general formula (1) as mentioned above).

(14) Benzimidazol derivatives or salts

5 thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3 is an indolinyl group (wherein the substituents of the indolinyl group are the same as defined in the general
10 formula (1) as mentioned above).

(15) Benzimidazol derivatives or salts

thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3
15 is a 1H-indazolyl group (wherein the substituents of the 1H-indazolyl group are the same as defined in the general formula (1) as mentioned above).

(16) Benzimidazol derivatives or salts

thereof represented by the general formula (1), wherein
20 R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3 is a 2(1H)-quinolinonyl group (wherein the substituents of the 2(1H)-quinolinolyl group are the same as defined in general formula (1) as mentioned above).

(17) Benzimidazol derivatives or salts

25 thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3

is a 3,4-dihydro-2(1H)-quinolinonyl group (wherein the substituents of the 3,4-dihydro-2(1H)-quinolinonyl group are the same as defined in the general formula (1) as mentioned above).

5 (18) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a hydrogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3 is a 3,4-dihydro-1,4(2H)-benzoxazinyl group (wherein
10 the substituents of the 3,4-dihydro-1,4(2H)-benzoxazinyl group are the same as defined in the general formula (1) as mentioned above).

 (19) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein
15 R^1 is a halogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3 is an indolyl group (wherein the substituents of the indolyl group are the same as defined in the general formula (1) as mentioned above).

20 (20) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R^1 is a halogen atom; R^2 is the same as defined in the general formula (1) as mentioned above; n is 1, and R^3 is an indolinyl group (wherein the substituents of the
25 indolinyl group are the same as defined in the general formula (1) as mentioned above).

 (21) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein

R¹ is a halogen atom; R² is the same as defined in the general formula (1) as mentioned above; n is 1, and R³ is a 1H-indazolyl group (wherein the substituents of the 1H-indazolyl group are the same as defined in the general formula (1) as mentioned above).

(22) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R¹ is a halogen atom; R² is the same as defined in the general formula (1) as mentioned above; n is 1, and R³ is a 2(1H)-quinolinonyl group (wherein the substituents of the 2(1H)-quinolinonyl group are the same as defined in the general formula (1) as mentioned above).

(23) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R¹ is a halogen atom; R² is the same as defined in the general formula (1) as mentioned above; n is 1, and R³ is a 3,4-dihydro-2(1H)-quinolinonyl group (wherein the substituents of 3,4-dihydro-2(1H)-quinolinonyl group are the same as defined in the general formula (1) as mentioned above).

(24) Benzimidazol derivatives or salts thereof represented by the general formula (1), wherein R¹ is a halogen atom; R² is the same as defined in the general formula (1) as mentioned above; n is 1, and R³ is a 3,4-dihydro-1,4(2H)-benzoxazinyl group (wherein the substituents of 3,4-dihydro-1,4(2H)-benzoxazinyl group are the same as defined in the general formula (1) as mentioned above).

The concrete examples of various substituents as defined in R^1 , R^2 , R^3 , A, B, R^4 , R^5 and R^6 as shown in the general formula (1) are as follows.

As to the halogen atom, such as a fluorine atom, a chlorine atom, a bromine atom and iodine atom can be exemplified.

As to the phenyl-lower alkyl group, a phenyl-alkyl group in which the alkyl moiety is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, and said alkyl group having 1 to 2 phenyl groups, such as a benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 1,1-dimethyl-2-phenylethyl, 2-methyl-3-phenylpropyl, diphenylmethyl and 2,2-diphenylethyl groups can be exemplified.

As to the lower alkylene group, a straight- or branched-chain alkylene group having 1 to 6 carbon atoms, such as a methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylenemethylene, ethylenemethylene, tetramethylene, pentamethylene and hexamethylene groups can be exemplified.

As to the 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring having 1 to 4 nitrogen atoms, oxygen atoms or sulfur atoms as the hetero atoms, such as pyrrolidinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, pyridyl, homopiperazinyl, 1,2,5,6-tetrahydropyridyl,

thienyl, quinolinyl, 1,4-dihydroquinolinyl, benzo-
thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl,
pyrrolyl, carbostyryl, 3,4-dihydrocarbostyryl, 1,2,3,4-
tetrahydroquinolinyl, indolyl, isoindolyl, indolinyl,
5 benzimidazolyl, benzoxazolyl, imidazolidinyl,
isoquinolinyl, quinazolidinyl, 1,2,3,4-tetrahydroiso-
quinolinyl, 1,2-dihydroisoquinolinyl, quinoxalinyl,
cinnolinyl, phthalazinyl, 1,2,3,4-tetrazolyl, 1,2,4-
triazolyl, chromanyl, isoindolinyl, isochromanyl,
10 pyrazolyl, imidazolyl, pyrazolidinyl, imidazo[1,2-a]-
pyridyl, benzofuryl, 2,3-dihydrobenzo[b]furyl,
benzothienyl, 1-azacycloheptyl, 4H-chromenyl,
1H-indazolyl, 2-imidazolinyl, 2-pyrrolinyl, furyl,
oxazolyl, oxazolidinyl, isoxazolyl, thiazolyl,
15 isothiazolyl, pyranyl, pyrazolidinyl, 2-pyrazolinyl,
quinuclidinyl, 1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-
benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl,
1,4-benzothiazinyl, 1,2,3,4-tetrahydroquinoxalinyl,
1,3-dithia-2,4-dihydronaphthalenyl, tetrahydro-1,3-
20 oxazinyl, tetrahydroxazolyl and 1,4-dithianaphthalenyl
groups can be exemplified.

As to the heterocyclic group having 1 to 3
substituents selected from the group consisting of a
lower alkyl group, a lower alkoxy group, a halogen atom
25 and an oxo group, a heterocyclic group having 1 to 3
substituents selected from the group consisting of a
straight- or branched-chain alkyl group having 1 to 6
carbon atoms, a straight- or branched-chain alkoxy

group having 1 to 6 carbon atoms, a halogen atom and an oxo group, such as 1-oxo-1,2,3,4-tetrahydroisoquinolinyl, 2-oxopiperidinyl, 2-oxo-1-azacycloheptyl, 2-oxopyrrolidinyl, 1,3-dioxoisindolinyl, 2,4-dioxoimidazolidinyl, 2-oxooxazolidinyl, 1-methylimidazolyl, 1-propylimidazolyl, 4-methylimidazolyl, 5,6-dimethylbenzimidazolyl, 1,4-dimethylpyrrolyl, 2-isopropylimidazolyl, 4-methylpiperazinyl, 4-phenylpiperidinyl, 4-methylthiazolyl, 2-oxothiazolyl, 5-ethylthiazolyl, 4-phenylthiazolyl, 4-propylthiazolyl, 5-butylthiazolyl, 4-pentylthiazolyl, 2-hexylthiazolyl, 3,5-dimethylisoxazolyl, 4,5-dimethylthiazolyl, 5-methoxy-4-methylthiazolyl, 1-ethylimidazolyl, 4-propylimidazolyl, 5-butylimidazolyl, 1-pentylimidazolyl, 1-hexylimidazolyl, 1,4-dimethylimidazolyl, 1,4,5-trimethylimidazolyl, 1-methoxyimidazolyl, 2-ethoxyimidazolyl, 5-propoxyimidazolyl, 1-methyl-4-chloroimidazolyl, 4,5-dichloroimidazolyl, 3-methyl-1,2,4-triazolyl, 5-ethyl-1,2,4-triazolyl, 3-methyl-1,2,4-triazolyl, 2-oxo-1-methylimidazolyl, 2-oxoimidazolyl, 2-ethylpyrrolyl, 3-propylpyrrolyl, 5-butylpyrrolyl, 4-pentylpyrrolyl, 2-hexylpyrrolyl, 2,4,5-trimethylpyrrolyl, 2-bromopyrrolyl, 2,5-dibromopyrrolyl, 2-methyl-5-methoxypyrrolyl, 2-oxopyrrolyl, 1-methyl-1,2,3,4-tetrazolyl, 1-isopropyl-1,2,3,4-tetrazolyl, 1-ethyl-1,2,3,4-tetrazolyl, 1-propyl-1,2,3,4-tetrazolyl, 1-butyl-1,2,3,4-tetrazolyl, 1-pentyl-1,2,3,4-tetrazolyl, 1-hexyl-1,2,3,4-tetrazolyl,

5-methoxyindolyl, 2-methylpyridyl, 3-ethylpyridyl,
4-propylpyridyl, 2-butylpyridyl, 3-pentylpyridyl,
4-hexylpyridyl, 2-methoxypyridyl, 3-phenylpyridyl,
4-phenylpyridyl, 2,4-dimethylpyridyl, 2,4,6-
5 trimethylpyridyl, 2-methyl-4-chloropyridyl, 2,4-
difluoropyridyl, 2,4,6-trichloropyridyl, 2-oxopyridyl,
4-oxopyridyl, 4-methyl-2-oxopyridyl, 2-chloro-4-
oxopyridyl, 3-methylimidazo-[1,2-a]pyridyl, 4-
ethylimidazo[1,2-a]pyridyl, 3-methoxyimidazo-
10 [1,2-a]pyridyl, 5-chloroimidazo[1,2-a]pyridyl,
3-methyl-1H-indazolyl, 3-iodo-1H-indazolyl,
1-methyl-1,2,3,4-tetrahydroisoquinolyl, 5-ethyl-
1,2,3,4-tetrahydroisoquinolyl, 6-bromo-1,2,3,4-
tetrahydroisoquinolyl, 1-oxo-6-methyl-1,2,3,4-
15 tetrahydroisoquinolyl, 1-oxo-7-methoxy-1,2,3,4-
tetrahydroisoquinolyl, 3,4-dimethylpiperazinyl,
3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 1-methyl-
pyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butyl-
piperidinyl, 3-pentylmorpholino, 4-hexylpiperazinyl,
20 3-methylthiomorpholino, 3-chloropyrrolidinyl,
2-oxo-4-methylpiperidinyl, 2-oxo-3-methylpyrrolidinyl,
2-oxo-4-fluoropiperidinyl, 4-methyl-1-azacycloheptyl,
5-methoxy-1-azacycloheptyl, 6-methyl-2-oxo-1-azacyclo-
heptyl, 1-methyl-2-oxoimidazolidinyl, 1-isobutyl-2-
25 oxoimidazolidinyl, 1-methyl-2-oxoimidazolidinyl,
2-oxotetrahydro-1,3-oxazinyl, 3-bromo-2-oxo-1-
azacycloheptyl, 2-oxo-tetrahydrooxazolyl, 3-chloro-
pyridyl, 4-methylpiperazinyl, 4-isobutylpiperazinyl,

4-methylhomopiperazinyl, 3-chloropiperazinyl, 4-methoxypiperazinyl and 4-ethylhomopierazinyl groups can be exemplified.

As to the lower alkoxy group, a straight- or
5 branched-chain alkoxy group having 1 to 6 carbon atoms, such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy and hexyloxy groups can be exemplified.

As to the lower alkyl group, a straight- or
10 branched-chain alkyl group having 1 to 6 carbon atoms, such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl groups can be exemplified.

As to the cycloalkyl group, a cycloalkyl
15 group having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups can be exemplified.

As to the isooxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, an
20 isooxazolylcarbonyl group which may have 1 to 3 straight- or branched-chain alkyl groups having 1 to 6 carbon atoms as the substituents, such as isooxazolylcarbonyl, 3,5-dimethylisooxazolylcarbonyl, 3-methylisoxazolylcarbonyl, 4-ethylisooxazolylcarbonyl,
25 5-propylisooxazolylcarbonyl, 3-butyliisooxazolylcarbonyl, 4-pentylisooxazolylcarbonyl, 5-hexylisooxazolylcarbonyl and 3,4,5-trimethylisooxazolylcarbonyl groups can be exemplified.

As to the amino-substituted lower alkyl group which may have lower alkyl groups as the substituents, an amino-substituted straight- or branched-chain alkyl group having 1 to 6 carbon atoms, which may have 1 to 2
5 straight- or branched-chain alkyl group having 1 to 6 carbon atoms as the substituents, such as an amino-methyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl, 1,1-dimethyl-2-aminoethyl, 2-methyl-3-aminopropyl, methyl-
10 aminomethyl, 1-ethylaminoethyl, 2-propylaminoethyl, 3-isopropylaminopropyl, 4-butylaminobutyl, 5-pentylaminopentyl, 6-hexylaminohexyl, dimethylaminomethyl, 2-diethylaminoethyl, 2-dimethylaminoethyl, (N-ethyl-N-propylamino)methyl and 2-(N-methyl-N-hexylamino)ethyl
15 groups can be exemplified.

As to the 5- to 6-membered saturated heterocyclic group formed by combining R⁵ and R⁶ together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen
20 atom, such as pyrrolidinyl, piperidinyl, piperazinyl and morpholino groups can be exemplified.

As to the said heterocyclic group having 1 to 3 substituents selected from the group consisting of a hydroxyl group and a phenyl group, such as 4-phenyl-
25 4-hydroxypiperidinyl, 4-phenylpiperazinyl, 3-phenylpiperazinyl, 3-hydroxypyrrolidinyl, 4-hydroxypiperazinyl, 3-phenylmorpholino, 2,4-diphenylpiperazinyl, 3-phenylpyrrolidinyl, 2,3,4-triphenyl-

piperazinyl, 3-hydroxymorpholino, 2-phenyl-2-hydroxymorpholino and 3-phenyl-3-hydroxypiperazinyl groups can be exemplified.

As to the lower alkenyl group, a straight- or
5 branched-chain alkenyl group having 2 to 6 carbon atoms, such as a vinyl, allyl, 2-butenyl, 3-butenyl, 1-methylallyl, 2-pentenyl and 2-hexenyl groups can be exemplified.

As to the lower alkoxycarbonyl group, a
10 straight- or branched-chain alkoxycarbonyl group having 1 to 6 carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl groups can be exemplified.

As to the phenoxy-lower alkyl group which may
15 have cyano groups as the substituents on the phenyl ring, a phenoxy group-substituted straight- or branched-chain alkyl group having 1 to 6 carbon atoms, which may have 1 to 3 cyano groups as the substituents
20 on the phenyl ring, such as a phenoxymethyl, 2-phenoxyethyl, 1-phenoxyethyl, 4-phenoxybutyl, 5-phenoxypropyl, 6-phenoxyhexyl, 1,1-dimethyl-2-phenoxyethyl, 2-methyl-3-phenoxypropyl, (2-cyanophenoxy)methyl, 2-(2-cyanophenoxy)ethyl, 3-phenoxypropyl, 4-(3-cyanophenoxy)-
25 butyl, 5-(2-cyanophenoxy)pentyl, 6-(3-cyanophenoxy)-hexyl, (4-cyanophenoxy)methyl, 3-(2-cyanophenoxy)-propyl, 3-(3-cyanophenoxy)propyl, 1-(3-cyanophenoxy)-ethyl, 3-(3,4-dicyanophenoxy)propyl and 2-(3,4,5-tri-

cyanophenoxy)ethyl groups can be exemplified.

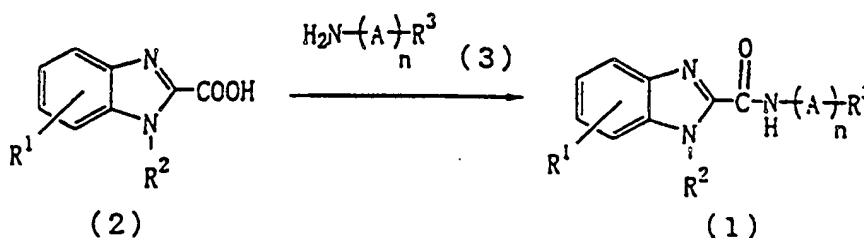
As to the halogen atom-substituted lower alkyl group, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, having 1 to 3 halogen atoms as the substituents, such as trifluoromethyl, tri-chloromethyl, chloromethyl, bromomethyl, fluoromethyl, iodomethyl, difluoromethyl, dibromomethyl, 2-chloro-ethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 3-bromopropyl, 3-chloropropyl, 2,3-dichloropropyl, 4,4,4-trichlorobutyl, 4-fluorobutyl, 5-chloropentyl, 3-chloro-2-methylpropyl, 5-bromohexyl and 5,6-dichloro-hexyl groups can be exemplified.

As to the lower alkoxy carbonyl group-substituted lower alkyl group, a straight- or branched-chain alkoxy carbonyl alkyl group in which the alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, and the alkoxy-carbonyl moiety is a straight- or branched-chain alkoxy carbonyl group having 1 to 6 carbon atoms, such as methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxycarbonylmethyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-propoxycarbonylhexyl, 1,1-dimethyl-2-butoxycarbonyl-ethyl, 2-methyl-3-tert-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl and hexyloxycarbonylmethyl groups can be exemplified.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The benzimidazole derivatives of the present invention can be prepared by various methods, for example they can be prepared by the methods of Reaction formula-1 through Reaction formula-4 as follows.

Reaction formula-1



[wherein R^1 , R^2 , R^3 , A and n are the same as defined above.]

The method as shown in Reaction formula-1 is the reaction of a benzimidazole compound (a carboxylic acid) of the formula (2) with an amine of the formula (3) by a common amide bond formation reaction. The acid amide bond formation reaction can easily be carried out by the reaction conditions of amide bond formation known in the art. For example, (a) a mixed-acid anhydrides method: i.e., a method by reacting a carboxylic acid (2) with an ester of alkylhalocarboxylate to form a mixed-acid anhydride, then by reacting it with an amine (3); (b) an activated ester method: i.e., a method by changing a carboxylic

acid (2) to an activated ester form, e.g., p-nitro-phenyl ester, N-hydroxysuccinimide ester, 1-hydroxy-benzotriazole ester, or the like, then by reacting the activated ester with an amine (3); (c) a carbodiimide method: i.e., a method by reacting a carboxylic acid (2) with an amine (3) in the presence of an activating agent, e.g., dicyclohexylcarbodiimide, carbonyldiimidazole or the like; (d) other method; for example, a method by changing a carboxylic acid (2) with a dehydrating agent, e.g., acetic anhydride to form carboxylic acid anhydride, then by reacting said acid anhydride with an amine (3); a method by reacting an ester of a carboxylic acid (2) and a lower alcohol, with an amine (3) at an elevated temperature; a method by reacting a acid halogenide of a carboxylic acid (2), e.g., a carboxylic acid halide, with an amine (3), and the like can be exemplified.

The mixed acid anhydride, which is used in the above-mentioned a mixed-acid anhydrides method, can be prepared by a method similar to that employed in common Schotten-Baumann reaction, said mixed-acid anhydride is used without being isolated from the reaction system, and reacted with an amine (3) to obtain a benzimidazole compound of the general formula (1) of the present invention. The above-mentioned Schotten-Baumann reaction is carried out in the presence of a basic compound. As to the basic compound to be used in the reaction, usual basic compounds used

in Schotten-Baumann reaction, for example organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, 1-methyl-2-pyrrolidinone (NMP), N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and the like, and inorganic bases such as potassium carbonate, sodium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate and the like can be exemplified.

10 Said reaction is generally carried out at about -20 to 100°C, preferably at about 0 to 50°C, and the reaction time is about 5 minutes to 10 hours, preferably about 5 minutes to 2 hours. The reaction of the thus obtained mixed acid anhydride with an amine (3) is

15 carried out at about -20 to 150°C, preferably at about 10 to 50°C, and the reaction time is about 5 minutes to 10 hours, preferably about 5 minutes to 5 hours. Generally, the mixed-acid anhydride method is carried out in a solvent. As to the solvent to be used for the

20 reaction, any solvent commonly used for the mixed-acid anhydride method can be used, specifically halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, p-chlorobenzene, toluene, xylene and the like; ethers

25 such as diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; aprotic polar solvents such as N,N-dimethylformamide, dimethyl

sulfoxide, acetonitrile, hexamethylphosphoric triamide and the like; and mixed solvents thereof can be exemplified. As to the alkylhalocarboxylic acid ester used in the mixed-acid anhydride method, methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate and the like can be exemplified. Ratio of the amounts of a carboxylic acid (2), an alkylhalocarboxylic acid ester and an amine (3) used in said method may be equimolar quantities, respectively, and within the range of about 1 to 1.5 times the molar quantities of the alkylhalocarboxylic acid ester and the carboxylic acid (2), respectively, can be used to 1 molar quantity of the amine (3).

Among the methods (d), in case of using the method by reacting carboxylic acid halide with an amine (3), said reaction can be carried out, in the presence of a basic compound, in a suitable solvent. As to the basic compound to be used, known compound selected from a wide range can be used, for example in addition to the basic compounds used in the Schotten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride and the like can be exemplified. As to the solvent to be used in the reaction, for example in addition to the solvents used in the above-mentioned mixed acid anhydride method, alcohols such as methanol, ethanol, propanol, butanol 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve and the

like; pyridine, acetone, water can be exemplified. Ratio of the amount of amine (3) and to the amount of carboxylic acid halide is not specifically restricted and can be suitably selected from a wide range, generally, at least about an equimolar quantity, preferably about an equimolar to 5 times the molar quantity of the latter may be used to the former. Generally, said reaction is carried out at about -20 to 180°C, preferably at about 0 to 150°C, and generally, the reaction is completed within for about 5 minute to 30 hours.

Furthermore, the amide bond formation reaction shown in the above-mentioned Reaction formula-1 can also be carried out by reacting a carboxylic acid (2) with an amine (3), in the presence of a phosphorus compound as a condensing agent, such as phenylphosphin-2,2'-dithiopyridine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramidate chloridate, diethylchlorophosphate, diethyl cyanophosphate, diphenylphosphoric acid azide or bis(2-oxo-3-oxazolidinyl)phosphinic chloride, as a condensing agent.

Said reaction is carried out, in the presence of the solvent and the basic compound used in the reaction of the above-mentioned carboxylic acid halide with an amine (3) generally at about -20 to 150°C, preferably at about 0 to 100°C, and the reaction is generally completed within about 5 minute to 30 hours. The amounts of the condensing agent and the carboxylic acid

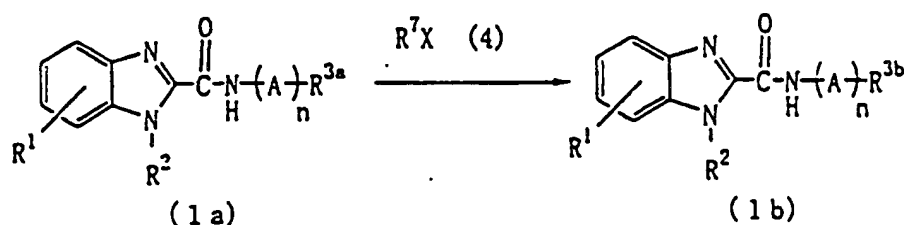
(2) may be about equimolar quantity, preferably about equimolar to 2 times the molar quantity, respectively to the amount of the amine (3).

The reaction as shown in Reaction formula-1
5 can also be carried out by reacting an ester of carboxylic acid (2) and a lower alcohol with an amine (3) in a solvent or without solvent, and in the presence or absence of a basic compound. Generally, the reaction is carried out at about room temperature
10 to 200°C, preferably at about room temperature to 120°C and generally, the reaction is completed within 30 minutes to 5 hours. The amine (3) is used in an amount at least 0.5 times the molar quantity, preferably 0.5 to 3 times the molar quantity to an equimolar quantity
15 of the ester of carboxylic acid (2) and a lower alcohol. As to the solvent to be used in this reaction, any solvent used in the above-mentioned reaction of a carboxylic acid halide with an amine (3) can also be used. As to the basic compound to be used in this
20 reaction, in addition to the basic compounds used in the above-mentioned method for reacting an carboxylic acid halide with an amine (3), for example an alkali metal alcoholate, such as sodium methyllate, sodium ethyllate, potassium methyllate, potassium
25 ethyllate or the like can be exemplified.

The reaction as shown in Reaction formula-1 can also be carried out by reacting, in a suitable solvent, an aluminum compound such as lithium aluminum

hydride, trimethyl aluminum and the like as a condensing agent with an amine (3), then reacting the resulting reaction product with an ester of carboxylic acid (2) and a lower alcohol. As to the solvent used in this reaction, ethers such as dioxane, diethyl ether, diglyme, tetrahydrofuran and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as cyclohexane, heptane, hexane and the like; and the mixtures of these solvents can be exemplified. The amine (3) may be used at least in an equimolar quantity, preferably in an equimolar to 5 times the molar quantity of the ester of the carboxylic acid (2) and lower alcohol. The condensing agent may be used at least in an equimolar quantity, preferably in an equimolar to 1.5 times the molar quantity of the ester of the carboxylic acid (2) and lower alcohol. The reaction of the condensing agent with the amine (3) is generally carried out at about -80 to 100°C, and the reaction is generally completed within for about 30 minutes to 20 hours. The subsequent ester reaction of the carboxylic acid (2) with the lower alcohol is carried out generally at room temperature to 200°C, preferably at about room temperature to 150°C, and the reaction is generally completed within 1 to 10 hours.

Reaction formula-2



[wherein R^1 , R^2 , A and n are the same as defined above;

R^{3a} is a heterocyclic group as defined

5 in R^3 which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-\text{B}-\text{R}^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may
 10 have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group;

further R^{3a} is a heterocyclic group as defined in R^3 , having a group of the formula $-\text{NH}-$ in
 15 said heterocyclic group:

R^{3b} is a heterocyclic group as defined in R^3 which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-\text{B}-\text{R}^4$ (B and R^4 are the same as
 20 defined above); a lower alkenyl group; a lower alkoxy-

carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy carbonyl substituted-lower alkyl group;

5 further R^{3b} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^7)-$ (R^7 is a group of the formula $-B-R^4$ (wherein B and R^4 are the same as defined above); a lower alkenyl group, a lower alkoxy carbonyl group; a phenoxy-lower alkyl group
10 which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; or a lower alkoxy carbonyl substituted-lower alkyl group) in said heterocyclic group; X is a halogen atom, a lower alkanesulfonyloxy group, an arylsulfonyloxy
15 group or an aralkylsulfonyloxy group].

As to the lower alkanesulfonyloxy group, specifically methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy, isopropanesulfonyloxy, butanesulfonyloxy, tert-butanesulfonyloxy, pentanesulfonyloxy
20 and hexanesulfonyloxy groups and the like can be exemplified. As to the arylsulfonyloxy group, specifically substituted or unsubstituted arylsulfonyloxy groups such as phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 3-chloro-
25 phenylsulfonyloxy and α -naphthylsulfonyloxy groups and the like can be exemplified.

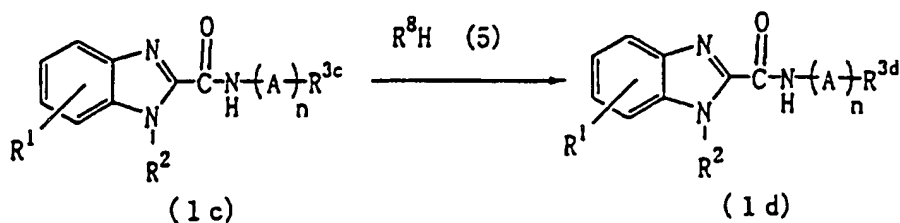
As to the aralkylsulfonyloxy group, specifi-

cally substituted or unsubstituted aralkylsulfonyloxy groups such as benzylsulfonyloxy, 2-phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-chloro-
5 benzylsulfonyloxy and α -naphthylmethylsulfonyloxy groups can be exemplified.

The reaction of a compound (1a) with a compound (4) is carried out, generally in a suitable
10 inert solvent, in the presence or absence of a basic substances. As to the inert solvent, for example aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethylene glycol dimethyl ether and the like;
15 halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and the like; lower alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol and the like; acetic acid, ethyl acetate, acetone, acetonitrile, pyridine, dimethyl
20 sulfoxide, dimethylformamide, hexamethylphosphoric triamide; and mixtures of these solvents can be exemplified. As to the basic substances, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the
25 like; metal hydroxide such as sodium hydroxide, potassium hydroxide and the like; sodium hydride, potassium metal, sodium metal, sodium amide; metal alcoholates such as sodium methylate, sodium ethylate and the like;

organic bases such as pyridine, N-ethyldiisopropyl-
 amine, dimethylaminopyridine, triethylamine, 1,5-
 diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo-
 [5.4.0]undecene-7 [DBU], 1,4-diazabicyclo[2.2.2]octane
 5 (DABCO) and the like can be exemplified. Ratio of the
 amounts of compound (1a) and compound (4) is not
 specifically restricted and can be selected from
 a wide range, generally at least about an equimolar
 quantity, preferably about an equimolar to 10 times the
 10 molar quantities of the latter may be used to the
 former. The reaction is generally carried out at about
 0 to 200°C, preferably at about 0 to 170°C, and
 generally, the reaction is completed within 30 minutes
 to 75 hours. Alkali metal halogenides such as sodium
 15 iodide, potassium iodide; or copper metal powder may be
 added to the reaction system.

Reaction formula-3



[wherein R^1 , R^2 , A and n are the same as defined
 20 above;

R^{3c} is a heterocyclic group as defined in R^3 ,

which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$, (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group;

further R^{3c} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^9)-$ (R^9 is a halogen substituted-lower alkyl group) in said heterocyclic group;

R^{3d} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group;

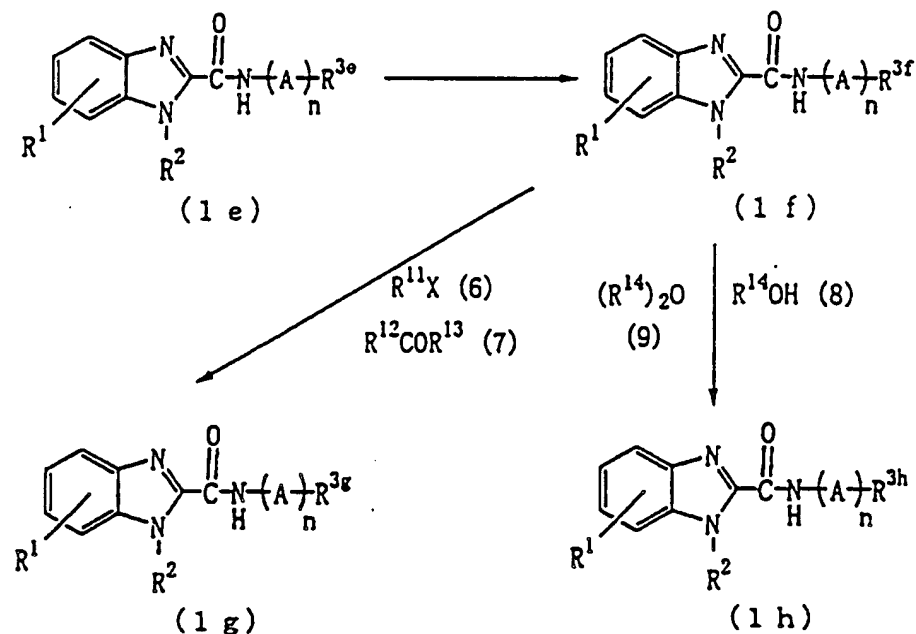
further, R^{3d} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^{10})-$ (R^{10} is a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); or a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring) in said heterocyclic group;

R^8 is a group of the formula $-R^{4a}$ (R^{4a} is a

heterocyclic group as defined in R^4 , having at least one group of the formula $-N<$ in said heterocyclic group, or a group of the formula $-NR^5R^6$ (R^5 and R^6 are the same as defined above); or a phenoxy group which may have cyano groups as the substituents in the phenyl ring].

The reaction of a compound (1c) with a compound (5) is carried out under the reaction condition similar to the reaction condition of a compound (1a) with a compound (4) in the above-mentioned Reaction formula-2.

Reaction formula-4



[wherein R^1 , R^2 , \underline{A} and \underline{n} are the same as defined above;

R^{3e} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

- 5 a group of the formula $-B-R^4$ (\underline{B} and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a
10 lower alkoxy-carbonyl substituted-lower alkyl group;

further R^{3e} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^{15})-$, (R^{15} is a phthalimide substituted-lower alkyl group) in said heterocyclic group;

- 15 R^{3f} is a heterocyclic group as defined in R^3 which may have 1 to 2 substituents selected from the group consisting of:

- a group of the formula $-B-R^4$ (\underline{B} and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may
20 have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group;

- further R^{3f} is a heterocyclic group as
25 defined in R^3 , having a group of the formula $-N(R^{16})-$ (R^{16} is an amino group-substituted lower alkyl group) in the heterocyclic ring;

R^{3g} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$ (wherein B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group;

further R^{3g} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(B-NR^{5a}R^{11})-$ (B is the same as defined above; R^{5a} is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridylcarbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents; a pyrrolylcarbonyl group or an amino group substituted-lower alkyl group which may have lower alkyl groups as the substituents; R^{11} is a lower alkyl group, a cycloalkyl group or an amino group substituted-lower alkyl group which may have lower alkyl groups as the substituents) in said heterocyclic group;

R^{3h} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may

have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy carbonyl substituted-lower alkyl group;

further R^{3h} is a heterocyclic group as
5 defined in R^3 , having a group of the formula
 $-N(B-NR^{5a}R^{14})-$ (B and R^{5a} are the same as defined
above; and R^{14} is a pyridylcarbonyl group, an
isoxazolylcarbonyl group which may have 1 to 3 lower
alkyl groups as the substituents, or a pyrrolylcarbonyl
10 group) in said heterocyclic group;

R^{12} and R^{13} are each, a hydrogen atom or a
lower alkyl group, respectively].

The reaction for introducing a compound (1f)
from a compound (1e) can be carried out by reacting a
15 compound (1e) with hydrazine in a suitable solvent or
by hydrolysis of a compound (1e). As to the solvent
to be used in the reaction of a compound (1e) with
hydrazine, in addition to water, solvents similar to
those can be used in the reaction of a compound (1a)
20 with a compound (4) in the above-mentioned Reaction
formula-2 can be used. This reaction is carried out
generally at about room temperature to 120°C,
preferably at about 0 to 100°C, and the reaction is
generally completed within 0.5 to 15 hours. The amount
25 of hydrazine is at least about an equimolar quantity,
preferably an equimolar to 5 times the molar quantities
can be used to a compound (1e).

The above-mentioned hydrolysis reaction of a compound (1e) can be carried out in a suitable solvent or without solvent, in the presence of an acid or basic compound. As to the solvent to be used,

5 water, lower alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl ethyl ketone and the like; ethers such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether and the like; fatty acids such as acetic acid,

10 formic acid and the like; and mixtures of these solvents can be exemplified. As to the acid to be used, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic acid such as formic acid, acetic acid, aromatic sulfonic acid

15 such as p-toluenesulfonic acid and the like can be exemplified. As to the basic compound to be used, metal carbonates such as sodium carbonate, potassium carbonate and the like, metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide,

20 lithium hydroxide and the like can be exemplified. Generally, said reaction is suitably carried out at about room temperature to 200°C, preferably at about room temperature to 150°C, and generally the reaction is completed within about 10 minutes to 25 hours.

25 The reaction of a compound (1f) with a compound (8) is carried out under the reaction condition similar to that of employed in the reaction of a compound (2) with a compound (3) in the above-mentioned

Reaction formula-1.

The reaction of a compound (1f) with a compound (6) is carried out, generally in a suitable inert solvent, in the presence or absence of a basic substance. As to the inert solvent to be used in the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethylene glycol dimethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and the like; lower alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol and the like; acetic acid, ethyl acetate, acetone, acetonitrile, pyridine, dimethyl sulfoxide, dimethyl formamide, hexamethylphosphoric triamide; or mixtures of these solvents can be exemplified. As to the basic substances to be used in the reaction, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen-carbonate, potassium hydrogencarbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide; sodium hydride, potassium metal, sodium metal, sodium amide, metal alcoholates such as sodium methylate, sodium ethylate and the like; organic bases such as pyridine, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and the like can be exemplified. Ratio of the amounts of a compound (1f) to a compound

(6) is not specifically restricted, and can be selected from a wide range, at least about an equimolar quantity, preferably an equimolar to 10 times the molar quantities of the latter may be used to the former.

- 5 Said reaction is carried out generally, at about 0 to 200°C, preferably at about 0 to 170°C, and the reaction is completed within 30 minutes to 75 hours. Into the reaction system, an alkali metal halogenides such as sodium iodide, potassium iodide or the like, copper
10 powder may be added.

The reaction of a compound (1f) with a compound (7) is carried out without solvent or in a suitable solvent, in the presence of a reducing agent. As to the solvent to be used in the reaction, water;
15 alcohols such as methanol, ethanol, isopropanol and the like; acetonitrile; formic acid, acetic acid; ethers such as dioxane, diethyl ether, diglyme, tetrahydrofuran and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and mixtures of
20 these solvents can be exemplified. As to the reducing agent, formic acid, ammonium formate, alkali metal salts of fatty acid such as sodium formate; hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride and the
25 like; catalytic hydrogenation reducing agents such as palladium-black, palladium-carbon, platinum oxide, platinum black, Raney nickel and the like can be exemplified.

In case of using formic acid as a reducing agent, reaction temperature is generally at about room temperature to 200°C, preferably at about 50 to 150°C may be suitable, and the reaction is completed within about 1 to 10 hours. Formic acid may be used in a large excess amount against a compound (1f).

In case of using hydride reducing agent, reaction temperature is generally at about -30 to 100°C, preferably at about 0 to 70°C may be suitable, and the reaction is completed for about 30 minutes to 12 hours. Reducing agent may be used generally in about an equimolar to 20 times the molar quantities, preferably about 1 to 6 times the molar quantities to a compound (1f). Particularly, in case of using lithium aluminum hydride as the reducing agent, preferably ethers such as diethyl ether, dioxane, tetrahydrofuran, diglyme and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like may be used.

Furthermore, in case of using a catalytic hydrogenation reducing agent, the reduction is carried out in hydrogen gas atmosphere under about normal pressure to 20 atmospheric pressure, preferably about normal pressure to 10 atmospheric pressure, on the other hand in case of using reduction in the presence of a hydrogen donating agent such as formic acid, ammonium formate, cyclohexene, hydrazine hydrate or the like, the reducing reaction may be carried out at about -30 to 100°C, preferably at about 0 to 60°C, and

generally the reaction is completed within 1 to 12 hours. The catalytic hydrogenation reducing agent may be used generally in an amount of 0.1 to 40% by weight, preferably 1 to 20 % by weight to compound (1f). The
5 hydrogen donating agent may be used in an amount of a large excess quantity to compound (1f).

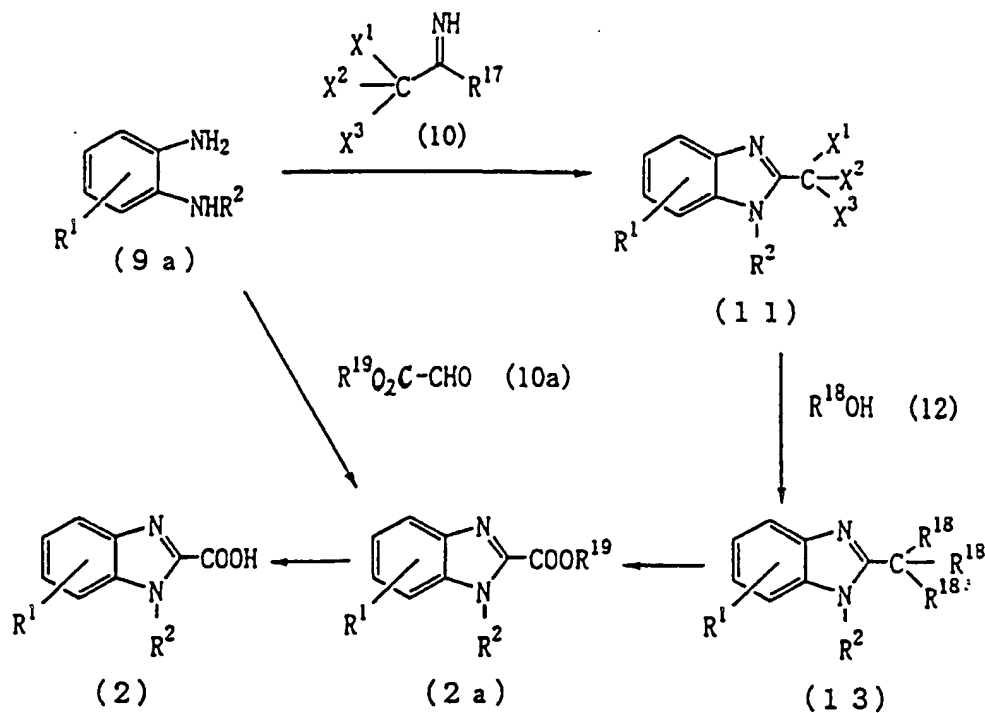
Compound (7) may be used, generally at least in an equimolar quantity, preferably an equimolar to a large excess quantity to compound (1f).

10 The reaction of compound (1f) with compound (9) is carried out without solvent or in a suitable solvent, in the presence or absence of a basic compound. As to the suitable solvent, for example aromatic hydrocarbons as previously mentioned; lower
15 alcohols such as methanol, ethanol, propanol and the like; dimethylformamide, dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetone, pyridine and the like can be used. As to the basic compound for
20 example, organic bases such as triethylamine, pyridine, sodium hydroxide, potassium hydroxide, sodium hydride and the like can be exemplified. The above-mentioned reaction can also be carried out in a solvent, such as acetic acid, in the presence of a mineral acid such as
25 sulfuric acid. Ratio of the amount of compound (9) may be used in an equimolar to a large excess quantity to the starting material, and the reaction is carried out generally at about 0 to 200°C, preferably at about 0 to

150°C, and the reaction is completed within 0.5 to 20 hours.

Compound (2) and compound (3) which are used for the starting materials are easily prepared by methods as shown in Reaction formula-5 through Reaction formula-9 as follows.

Reaction formula-5



10 [wherein R^1 and R^2 are the same as defined above; R^{17} is a lower alkoxy group; R^{18} is a lower alkoxy group; R^{19} is a lower alkyl group; X^1 , X^2 and X^3 are each hydrogen

atom, respectively].

The reaction of a compound (9a) with a compound (10) can be conducted in a suitable solvent in the presence of an acid. As to the solvent to be used
5 in the reaction, for example water, lower alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl ethyl ketone and the like; ethers such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether and the like; fatty acids such as
10 acetic acid, formic acid and the like; mixtures of these solvents, can be mentioned. As to the acid to be used in the reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic acids such as formic acid, acetic acid,
15 aromatic sulfonic acids such as p-toluenesulfonic acid can be exemplified. A compound (10) may be used at least in an equimolar quantity, preferably an equimolar to 2 times the molar quantities to a compound (9a). Said reaction is carried out preferably at about room
20 temperature to 200°C, desirably at about room temperature to 150°C, the reaction is generally completed within 0.5 to 5 hours.

The reaction of a compound (11) with a compound (12) is carried out under the reaction condition
25 similar to that employed in the reaction of a compound (1a) with a compound (4) in the above-mentioned Reaction formula-2. In the case, a compound (12) may be used as a solvent in a large excess quantity.

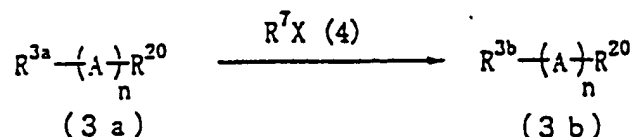
The reaction for introducing a compound (13) to a compound (2a), and the reaction for introducing a compound (2a) to a compound (2) are carried out under the reaction condition similar to that employed in the hydrolysis for introducing a compound (1e) to a compound (1f) among the reactions shown in the above-mentioned Reaction formula-4. The reaction of a compound (9a) with a compound (10a) is carried out under the reaction condition similar to that employed in the above-mentioned reaction of a compound (9a) with a compound (10), or is carried out in a suitable solvent, in the presence or absence of an acid, in the presence of an oxidizing agent. As to the solvent to be used therein, water; lower alcohol such as methanol, ethanol, isopropanol and the like; ethers such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether and the like; fatty acids such as acetic acid, formic acid and the like; n-hexane; aromatic hydrocarbons such as benzene, toluene and the like; and mixtures of these solvents can be exemplified. As to the oxidizing agent to be used therein, iodine, nitro compounds such as nitrobenzene; dehydrogenating catalysts such as palladium-carbon, can be exemplified.

A compound (10a) may be used generally at least in an equimolar quantity, preferably in an equimolar to 3 times the molar quantities to a compound (9a). An oxidizing agent may be used generally in 0.1 times the molar quantity or more, preferably 0.1 to 2

times the molar quantities. The reaction is completed within for about 10 minutes to 5 hours. The reaction temperature and the acid to be used are similar to the reaction conditions employed in the above-mentioned

5 reaction of a compound (9a) with a compound (10). In said reaction, when an oxidizing agent is added, then the desired compound (2a) of high purity can be obtained in high yield.

Reaction formula-6



10 [wherein R^{3a} , R^{3b} , A , n , R^7 and X are the same as defined above; R^{20} is an amino group or a group capable to convert into an amino group].

As to a group of R^{20} capable to convert into an amino group, groups which can be converted into an amino group by conventional method, e.g., reduction,

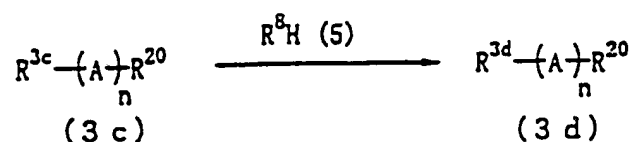
15 hydrolysis or the like, such as a nitro group, a cyano group, an azide group, a phthalimide group, can be exemplified.

The reaction of a compound (3a) with a com-

20 pound (4) is carried out under the reaction condition similar to that employed in the reaction of a compound

(1a) with a compound (4) in the above-mentioned
Reaction formula-2.

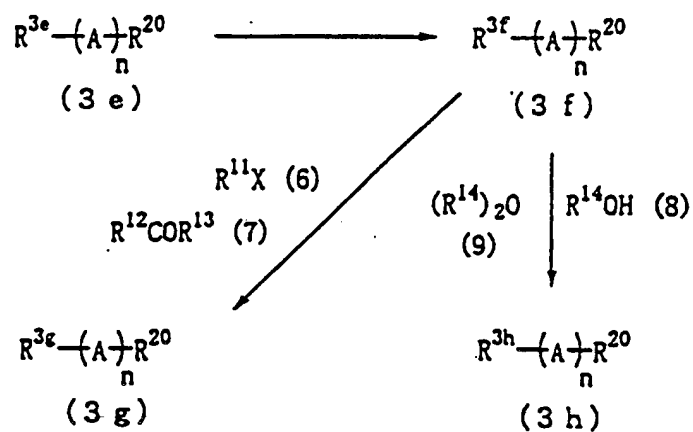
Reaction formula-7



[wherein R^{3c} , R^{3d} , A , n , R^{20} and R^8 are the same as
5 defined above.].

The reaction of a compound (3c) with a com-
pound (5) is carried out under the reaction condition
similar to that employed in the reaction of a compound
(1c) with a compound (5) in the above-mentioned
10 Reaction formula-3.

Reaction formula-8



[wherein R^{3e} , \underline{A} , \underline{n} , R^{20} , R^{3f} , R^{3g} , R^{3h} , R^{11} , R^{12} , R^{13} , R^{14} and X are the same as defined above].

The reaction for introducing a compound (3e) to a compound (3f) is carried out under the reaction condition similar to that employed in the reaction of a compound (1e) with a compound (1f) in the above-mentioned Reaction formula-4.

The reaction of a compound (3f) with a compound (6) or a compound (7) is carried out under the reaction condition similar to that employed in the reaction of a compound (1f) with a compound (6) or a compound (7) in the above-mentioned Reaction formula-4.

The reaction of a compound (3f) with a compound (8) or a compound (9) is carried out under the reaction condition similar to that employed in the reaction of a compound (1f) with a compound (8) or a compound (9) in the above-mentioned Reaction formula-4.

Each one of compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h) wherein R^{20} is nitro group, can be introduced to each one of the corresponding compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h) wherein R^{20} is amino group by reducing reaction. Said reducing reaction is carried out for example (i) by reducing each one of the former compounds in a suitable solvent by using a hydrogenation catalyst or (ii) by reducing each one of the former compounds in a suitable inert solvent, by using a chemical reducing agent such as a mixture of a metal or metal salt with

an acid; or a metal or metal salt with an alkali metal hydroxide, sulfide, ammonium salt; or a hydride reducing agent such as lithium aluminum hydride.

In case of conducting the above-mentioned
5 method of (i) by using the hydrogenation catalyst, as to the solvents for example, water, acetic acid, alcohols such as methanol, ethanol, isopropanol and the like; hydrocarbons such as hexane, cyclohexane and the like; ethers such as dioxane, tetrahydrofuran, diethyl
10 ether, diethylene glycol dimethyl ether and the like; esters such as ethyl acetate, methyl acetate and the like; aprotic polar solvents such as N,N-dimethylformamide and the like; and mixtures of these solvents can be exemplified. As to the catalyst to be used for
15 catalytic hydrogenation, palladium, palladium-black, palladium-carbon, platinum, platinum oxide, copper chromite, Raney nickel and the like can be exemplified. The catalyst may be used generally, in an amount of 0.02 to an equivalent quantity to the starting
20 material. The reaction is carried out generally at about -20 to 150°C, preferably at about 0 to 100°C, and under 1 to 10 atmospheric pressure of hydrogen gas, and the reaction is completed generally within 0.5 to 10 hours. Further, an acid such as hydrochloric acid may
25 be added to the reaction system.

In case of conducting method of (ii) as above, a mixture of iron, zinc, tin or stannous chloride with a mineral acid such as hydrochloric acid

or sulfuric acid; or iron, ferrous sulfate, zinc or tin with an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, ammonia water, an ammonium salt such as ammonium chloride; or a
5 hydride reducing agent such as lithium aluminum hydride may be used as a reducing agent. As to the inert solvent to be used in the reaction, water, acetic acid, methanol, ethanol, dioxane or the like may be exemplified. In case of using lithium aluminum hydride as the
10 reducing agent, ethers such as diethyl ether, dioxane, tetrahydrofuran, diglyme and the like may preferably be used as the solvent. The condition of the above-mentioned reducing reaction may be suitably selected in accordance with the reducing agent to be used, for
15 example, in case of using a mixture of stannous chloride with hydrochloric acid as the reducing agent, the reaction may be carried out advantageously at about 0 to 80°C, and for about 0.5 to 10 hours. The reducing agent is used at least in an equimolar quantity,
20 generally in an equimolar to 5 times the molar quantities to the starting compound.

Each one of compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R²⁰ is nitrile group can be introduced to each one of the corresponding
25 compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R²⁰ is amino group by reducing reaction. For this reducing reaction, a hydride reducing agent is preferably used. As to the hydride reducing agent,

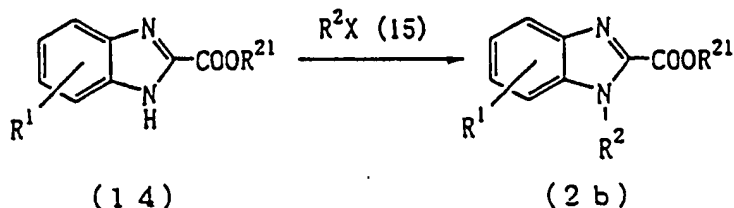
lithium aluminum hydride, lithium borohydride, sodium borohydride, diborane and the like can be exemplified. The reducing agent is used at least in an equimolar quantity, preferably in the range of an equimolar to 15 times the molar quantities to the starting compound. Said reducing reaction is carried out in a suitable solvent, for example water; lower alcohols such as methanol, ethanol, isopropanol and the like; ethers such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme and the like; and mixtures of these solvents, and generally at about -60 to 150°C, preferably -30 to 100°C, and for about 10 minutes to 15 hours. In case of using lithium aluminum hydride or diborane as the reducing agent, anhydrous solvents such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme and the like can be used as the solvent. Further, in case of using sodium borohydride as the reducing agent, the reaction is advantageously proceeded by adding a metal halide such as cobalt chloride or the like to the reaction system.

Each one of compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R²⁰ is a phthalimido group can be introduced to each one of the corresponding compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R²⁰ is an amino group by treating under the reaction condition similar to that of employed in the reaction for introducing compound (1e) to compound (1f) in the above-mentioned Reaction

formula-4.

Each one of compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R^{20} is an azido group can be introduced to each one of the corresponding compounds (3a), (3b), (3c), (3d), (3e), (3f), (3g) and (3h), wherein R^{20} is an amino group by treating under the condition similar to those employed in the above-mentioned reduction of nitro group by using a catalytic hydrogenation or reduction of nitrile group by using a hydride reducing agent.

Reaction formula-9



[wherein R^1 , R^2 and X are the same as defined above; R^{21} is a hydrogen atom or a lower alkyl group].

The reaction of a compound (14) with a compound (15) is carried out under the reaction condition similar to that employed in the reaction of a compound (1a) with a compound (4) as shown in the above-mentioned Reaction formula-2.

A compound represented by the general formula

(1), wherein R^3 is a substituted or unsubstituted 2(1H)-quinolinonyl group can be introduced to the corresponding compound wherein R^3 is a substituted or unsubstituted 3,4-dihydro-2(H)-quinolinonyl group when
5 the former is subjected to reducing reaction.

A compound represented by the general formula (1), wherein R^3 is a substituted or unsubstituted 3,4-dihydro-2(1H)-quinolinonyl group can be introduced to the corresponding compound wherein R^3 is a substituted
10 or unsubstituted 2(1H)-quinolinonyl group when the former is subjected to dehydrogenation reaction.

In carrying out the above-mentioned reducing reaction, a usual catalytic hydrogenation condition can be applied. As to the catalyst to be used in the reac-
15 tion, metal catalysts such as palladium, palladium-carbon, platinum, Raney-nickel and the like can be exemplified, and such a catalyst is used in usual catalytic quantity. Further, as to the solvent to be used in the reaction, alcohols such as methanol,
20 ethanol, isopropanol and the like; ethers such as dioxane, tetrahydrofuran and the like; aliphatic hydrocarbons such as hexane, cyclohexane and the like; esters such as ethyl acetate; fatty acids such as acetic acid can be exemplified. Said reducing reaction
25 can be carried out either under normal pressure or under high pressure condition, and generally about under normal pressure to 20 kg/cm², preferably under normal pressure to 10 kg/cm². The reaction may be

carried out generally at about 0 to 150°C, preferably at about room temperature to 100°C.

The above-mentioned dehydrogenation reaction is carried out in a suitable solvent, by using an oxidizing agent. As to the oxidizing agent, for example benzoquinones such as 2,3-dichloro-5,6-dicyanobenzoquinone, chloranil(2,3,5,6-tetrachlorobenzoquinone) and the like; N-bromosuccinimide, N-chlorosuccinimide, halogenating agents such as bromine and the like; dehydrogenation catalysts such as selenium dioxide, palladium-carbon, palladium-black, palladium oxide, Raney-nickel and the like can be exemplified. The amount of the halogenating agent is not specifically restricted, and can be suitably selected from a wide range, generally about 1 to 5 times, preferably 1 to 2 times the molar quantities may be used to the starting compound. The dehydrogenation catalyst may be used in a usual catalytic amount. As to the solvent, ethers such as dioxane, tetrahydrofuran, methoxyethanol, dimethoxyethanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene, cumene and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; alcohols such as butanol, amylalcohol, hexanol and the like; protic polar solvents such as acetic acid; aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric trimamide and the like can be

exemplified. Said reaction is carried out generally at about room temperature to 300°C, preferably at about room temperature to 200°C, and is completed generally for about 1 to 40 hours.

- 5 Among compounds represented by the general formula (1), a compound having acidic group can form a salt with pharmaceutically acceptable basic compound. As to such basic compound for example, metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium
- 10 hydroxide, calcium hydroxide and the like; carbonates or bicarbonates of alkali metals such as sodium carbonate, sodium hydrogencarbonate and the like; alkali metal alcoholates such as sodium methylete, potassium ethylete and the like can be exemplified.
- 15 Furthermore, among compounds represented by the general formula (1), a compound having basic group can form a salt with common pharmaceutically acceptable acid. As to such acid for example, inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid, hydro-
- 20 bromic acid and the like; organic acids such as acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid and the like can be mentioned. These salts can also be used, similar to
- 25 compounds represented by the general formula (1) in free form, as compounds of effective ingredient in the present invention. Moreover, compounds represented by the general formula (1) involve inevitably their

stereoisomers and optical isomers, and these isomers can also be used as compounds of effective ingredients.

The objective compounds prepared by each of these Reaction formulas-1 to -4 can be isolated from
5 the reaction system by common separating methods, and can be further purified. As to methods for separation and purification, for example, distillation, recrystallization, column chromatography, ion-exchange chromatography, gel chromatography, affinity chromatography,
10 preparative thin layer chromatography, solvent extraction and others can be applied.

POSSIBILITY OF INDUSTRIAL UTILIZATION

Benzimidazole derivatives represented by the general formula (1) are used for pharmaceuticals as in
15 the forms of usual general pharmaceutical preparations. Said pharmaceutical preparations are formulated by using usually used diluents such as fillers, bulking fillers, binders, wetting agents, disintegrants, surface active agents, lubricants; or excipients. The
20 pharmaceutical preparations can be selected from various administration forms in accordance with the therapeutic purposes. As to typical administration forms, there can be exemplified tablets, pills, powders, liquids, suspensions, emulsions, granules,
25 capsules, suppositories, injection preparations (liquids, suspensions, etc.) and the like. For the purpose of shaping the administration unit form into

the tablets, various carriers which are well-known in this field can be widely used. As to the examples of carriers, excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystal-line cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrants such as dry starch, sodium alginate, agar-agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, monoglyceride of stearic acid, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, cacao butter, hydrogenated oils and the like; absorption accelerators such as quaternary ammonium salts, sodium laurylsulfate and the like; wetting agents such as glycerin, starch and the like; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; lubricants such as refined talc, stearates, boric acid powder, polyethylene glycols and the like can be mentioned. The tablets preparations can be further shaped into tablets coated with usual tablet coating, for example sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coating, tablets coated with film coating, or double layer tablets and

multiple layer tablets. For the purpose of shaping the administration unit into pills, various carriers which are well-known in this field can be widely used. As to the examples of carriers, excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and the like; binders such as powdered acacia, powdered tragacanth, gelatin, ethanol and the like; disintegrants such as laminaran, agar-agar and the like can be exemplified. For the purpose of shaping the administration unit into suppositories, various carriers which are well-known in this field can be widely used. As to the examples of carriers, polyethylene glycols, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glycerides and the like can be mentioned. For the purpose of shaping the administration unit form into capsules, the benzimidazole derivative as the effective ingredient is mixed with the above-mentioned various carriers and the mixture thus obtained is placed into rigid gelatin capsules or soft capsules. For the purpose of shaping the administration unit into injection preparations, liquid preparations, emulsion preparations and suspension preparations are sterilized, further these preparations are preferably isotonic to the blood, and the all diluents which are conventionally used in this field can also be used for example, water, ethyl alcohol, macrogols, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated

isostearyl alcohol, polyoxyethylenesorbitan fatty acid esters can be used. Additionally, for the purpose to prepare isotonic injection solutions, an adequate amount of sodium chloride, glucose or glycerin may be added to the injection preparations, further, usual dissolving additives, buffering agents, local anesthetics and the like may be added. Moreover, if necessary, coloring agents, preservatives, spices, flavors, sweetening agents and others may be added to the pharmaceutical preparations.

The amount of the benzimidazol derivative as effective ingredient to be contained in the pharmaceutical preparation of the present invention is not specifically restricted and can be suitably selected from a wide range, and generally about 1 to 70 % by weight, preferably 5 to 50 % by weight of the active ingredient may be contained in the pharmaceutical preparations.

Methods for administering the pharmaceutical preparation of the present invention are not restricted, they can be administered in accordance with various forms of preparations, age of the patient, distinguish of sex and other conditions, the degree of the symptom and the like. For example, tablets, pills, liquids, suspensions, emulsions, granules and capsuled are administered orally. While, injection preparations are intravascularly administered, singly or by mixing with common transfusions such as glucose or amino acid

solutions, and if necessary, they are singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally. Suppositories are administered to the rectum.

5 Dose of pharmaceutical preparation of the present invention is suitably selected depend on the usage, age of the patient, distinguish of sex and other conditions, and degree of the symptom, and generally the amount of effective compound may be about 0.6 to 50
10 mg/kg of the body weight per day. The effective compound to be contained in the administration unit form may preferably be in the range of about 10 to 1000 mg.

 The amount of compound of the effective ingredient to be formulated in the pharmaceutical
15 preparation for external use of the present invention is not specifically restricted and can be suitably selected from a wide range, generally, 0.01 to 20 % by weight, preferably 0.1 to 5 % by weight thereof may be formulated.

20 As to the basic excipients used for external pharmaceutical preparations of the present invention, oily bases and water-soluble bases which are well known in this field can be selected from a wide range, provided that they show not any phamacological activities by themselves. As to the oily bases, specifically
25 oils and fats such as peanut oil, rubber oil, soybean oil, corn oil, rapeseed oil, cottonseed oil, castor oil, camellia oil, coconut oil, olive oil, cacao

butter, lanolin, beef tallow, squalane and wool fat and the like; chemically changed such as hydrogenated reformed products of these fats and oils; mineral oils such as vaseline, paraffin, silicone oil; higher fatty acid esters, such as isopropyl myristate, n-butyl myristate, isopropyl linolate, cetyl licinolate, stearyl licinolate, diethyl sebacate, disopropyl adipate; higher aliphatic alcohol such as cetyl alcohol, stearyl alcohol; waxes such as bleached beeswax, spermaceti, Japan wax and the like; higher aliphatic acid such as stearic acid, oleic acid, palmitic acid and the like; mixtures of mono-, di- and tri-glycerides of natural saturated fatty acid having 12 to 18 carbon atoms and the like can be exemplified.

Among these fats and oils, the various vegetable oils and the mixtures of mono-, di- and tri-glycerides are especially preferable. Furthermore, as to the water-soluble basic excipients, specifically polyethylene glycol, propylene glycol, glycerin, glycerogelatin, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyvinyl polymer, polyvinyl alcohol and the like can be exemplified. In the present invention, these basic excipients may be used singly or may be used by mixing with 2 or more of them.

In using the pharmaceutical preparations for external use of the present invention, commonly used additives such as water, surface active agents, gelling

agents, preservatives, antioxidant, buffering agents, pH controlling agents, wetting agents, antiseptics, coloring agents, fragrant agents and the like can be suitably added thereto in accordance with the
5 necessity.

The form of pharmaceutical preparations for external use of the present invention is not specifically restricted, and in the forms of an ointment, cream, lotions, emulsion and gel are preferably used,
10 such forms of them can be prepared in accordance with usual methods.

EXAMPLES

In order to explain more clearly, the present invention will be illustrated by referring to Examples
15 of pharmaceutical preparations, Reference examples, Examples and Pharmacological tests as follow.

Example of pharmaceutical preparation-1

| | | |
|----|---|-------|
| | 1-Benzyl-6-chloro-2-{1-[3-(1-pyrazolyl)propyl]indol-5- | |
| 20 | ylaminocarbonyl}benzimidazole | 150 g |
| | Avicel | |
| | (Trademark for microcrystalline cellulose, manufactured by Asahi Chemical Industry CO., Ltd.) | 40 g |
| 25 | Corn starch | 30 g |
| | Magnesium stearate | 2 g |

| | |
|------------------------------|------|
| Hydroxypropylmethylcellulose | 10 g |
| Polyethylene glycol 6000 | 3 g |
| Castor oil | 40 g |
| Ethanol | 40 g |

5

1-Benzyl-6-chloro-2-{1-[3-(1-pyrazolyl)-
propyl]indol-5-ylaminocarbonyl}benzimidazole of the
present invention, Avicel, corn starch and magnesium
stearate were mixed together and ground, the thus
10 obtained mixture was shaped into the form of tablets
by using a conventional pounder (R 10 mm) for sugar
coating. The thus obtained tablets were coated with
a film coating agent consisting of hydroxypropylmethyl
cellulose, poloxyethylene glycol 6000, castor oil and
15 ethanol to prepare film coated tablets.

Example of pharmaceutical preparation-2

| | | |
|----|---|---------|
| | 1-Benzyl-6-chloro-2-[1-isopropyl- tetrazol-5-yl)methyl-3,4-dihydro- 2(1H)-quinolinon-6-yl- aminocarbonyl]benzimidazole | 150.0 g |
| 20 | Citric acid | 1.0 g |
| | Lactose | 33.5 g |
| | Dicalcium phosphate | 70.0 g |
| | Pluronic F-68 | 30.0 g |
| 25 | Sodium laurylsulfate | 15.0 g |
| | Polyvinylpyrrolidone | 15.0 g |
| | Polyethylene glycol (Carbowax 1500) | 4.5 g |

68

| | | |
|---|-------------------------------------|--------|
| | Polyethylene glycol (Carbowax 6000) | 45.0 g |
| | Corn starch | 30.0 g |
| | Dried sodium stearate | 3.0 g |
| | Dried magnesium stearate | 3.0 g |
| 5 | Ethanol | q.s. |

1-Benzyl-6-chloro-2-[1-isopropyltetrazol-5-yl)methyl-3,4-dihydro-2(1H)-quinolinon-6-ylamino-carbonyl]benzimidazole, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate were
10 mixed together.

The thus obtained mixture was sieved through a sieve of No. 60, the obtained sieved mixture was granulated under wet condition with an alcohol solution containing polyvinylpyrrolidone, Carbowax 1500 and
15 6000. The granulated product was formed to paste like lump by adding ethanol, as occasion arises. Next, corn starch was added thereto and mixing operation of said mixture was continued until uniform granules were formed. The granules were sieved through a sieve of
20 No. 10, then the sieved granules were placed in a tray and dried at 100°C in an oven for 12 to 14 hours. The dried granules were sieved through a sieve of No. 16, then dried sodium laurylsulfate and dried magnesium stearylsulfate were added to the dried granules. The
25 whole mixture of dried granules were mixed well and were compressed, by using a tablet machine, into the desired shape of tablets to be used for the core

portions of coated tablets.

The above-mentioned core portions of the tablets were treated with a varnish, and the surface thereof were coated with talc powder for preventing from the absorption of moisture. The surface of the treated core portions were further coated with a primary coating layer, and were further coated with a varnish to make them having a sufficient number of layers on the surface for preparing coated tablets for oral administration. In order to make the coated core portions of tablets into complete spherical form and to make the treated surface smoothly, the coated tablets were further coated with primary coating layers and smoothing coating layers. The coated tablets were color coated until the desired color of the surface were obtained. After the coated tablets were dried, the surface thereof were polished to make them uniform gloss.

20 Example of pharmaceutical preparation-3

1-Benzyl-6-chloro-2-{1-[3-(imidazol-1-yl)propyl]indol-5-ylaminocarbonyl}-

| | | |
|----|-------------------------------------|-------|
| | benzimidazole | 5.0 g |
| 25 | Polyethylene glycol (M.W. 4000) | 0.3 g |
| | Sodium chloride | 0.9 g |
| | Polyoxyethylene sorbitan monooleate | 0.4 g |
| | Sodium metabisulfite | 0.1 g |

| | |
|-------------------------------|---------|
| Methylparaben | 0.18 g |
| Propylparaben | 0.02 g |
| Distilled water for injection | 10.0 ml |

The above-mentioned Methylparaben, Propyl-
5 paraben, sodium metabisulfite and sodium chloride were
dissolved in a half volume of the above-mentioned
distilled water at 80°C, under stirring. The solution
thus obtained was cooled to 40°C, then 1-benzyl-6-
chloro-2-{1-[3-(imidazole-1-yl)propyl]indol-5-
10 ylamincarbonyl}benzimidazole of the effective
ingredient of the present invention, next polyethylene
glycol and polyoxyethylene sorbitan monooleate were
dissolved in this order in the above-mentioned solu-
tion. Then to the thus obtained solution was added the
15 remaining volume of distilled water for injection to
adjust the final volume of the injection composition
into the predetermined volume, then was sterilized by
sterilizing filtration by using a suitable filter paper
to prepare injection preparation.

20

Reference example 1

To 100 ml of acetic acid solution containing
20 g of 2-benzylamino-4-chloroaniline was added 15 ml
of O-methyl-trichloroacetoimide at 0 to 25°C, and
25 stirred the mixture at room temperature for 3 hours.
Then water was added to the reaction mixture, the
separated crystals were collected by filtration to

obtain 29.6 g of 1-benzyl-6-chloro-2-trichloromethylbenzimidazole in the form of pale brown powder.

¹H-NMR (250 MHz, DMSO-d₆) δ ppm:

5.94 (2H, s), 7.04 (2H, d, J=6.5Hz),
5 7.25-7.5 (5H, m), 7.88 (1H, d, J=9.0Hz).

Reference example 2

Fifty (50) ml of methanol suspension containing 5 g of 1-benzyl-6-chloro-2-trichloromethylbenzimidazole and 7.7 g of potassium carbonate
10 was heated and refluxed for 24 hours. After the reaction mixture was filtrated, the solvent was removed by distillation under reduced pressure, the residue thus obtained was dissolved in chloroform, then after
15 removal of the insoluble matters by filtration, the solvent was removed by distillation to obtain 4.7 g of 1-benzyl-6-chloro-2-trimethoxymethylbenzimidazole in the form of brown oily substance. Said oily substance was dissolved in 50 ml of acetone, and 1 g of
20 p-toluenesulfonic acid was added, the mixture was refluxed for 2 hours, the solvent was removed under reduced pressure. The residue thus obtained was dissolved in chloroform, and the solution was washed with water, an aqueous solution saturated with sodium
25 hydrogencarbonate, then was dried with anhydrous magnesium sulfate, and the solvent was removed by distillation. The residue was crystallized by using diisopropyl ether-ethyl acetate to obtain 2.84 g of

methyl 1-benzyl-6-chlorobenzimidazole-2-carboxylate in the form of light brown powdery product.

Melting point: 184-186°C.

Reference example 3

5 To 4.4 g of 5-nitro-1-(3-phthalimidopropyl)-indole was added 200 ml of dimethylformamide, further was added 0.15 g of 10% palladium-carbon and hydrogenized at 65°C, under the pressure of 4 kg/cm², for 7 hours. After the reaction was finished, the
10 reaction mixture was filtrated, and the solvent was removed by distillation under reduced pressure. The thus obtained residue was treated to a silica column chromatography (eluent: 3% methanol/dichloromethane) to obtain 3.4 g of 5-amino-1-(3-phthalimidopropyl)indole
15 in the form of brown needle crystals.

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.16-2.28 (2H, m), 3.73 (2H, t, J=7Hz), 4.12
(2H, t, J=7Hz), 6.28 (1H, d, J=3Hz), 6.64-
6.69 (1H, m), 6.9 (1H, d, J=2Hz), 7.11-7.14
20 (2H, m), 7.7-7.73 (2H, m), 7.82-7.86 (2H, m).

By using suitable starting materials, and by method similar to that employed in Reference example 3, there were obtained compounds of Reference examples 15-22, 26-33, 47 and 49.

Reference example 4

To 2.3 g of lithium aluminum hydride was added 100 ml of tetrahydrofuran, under stirring condition, and 6 g of 5-cyano-1-[3-(2-isopropyl-
5 imidazol-1-yl)propyl]indole was gradually added thereto. The mixture was refluxed for 4 hours, then after confirmation of that the reaction was finished, under cooling at 0°C, 2.3 ml of water, 2.3 ml of 10% aqueous solution of potassium hydroxide and 7 ml of
10 water were gradually added thereto. The reaction mixture was diluted with ethyl acetate, then filtrated with Celite, and the solvent was removed by distillation, 5.3 g of 5-aminomethyl-1-[3-(2-isopropyl-imidazol-1-yl)propyl]indole was obtained in the form of
15 yellow oily product.

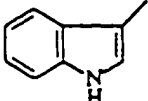
¹H-NMR (250MHz, CDCl₃) δ ppm:

1.22 (6H, d, J=7Hz), 2.3-2.4 (2H, m),
2.7-2.8 (2H, m), 3.81 (2H, t, J=7.5Hz),
3.95 (2H, s), 4.16 (2H, t, J=7Hz),
20 6.51 (1H, d, J=3Hz), 6.77 (1H, d, J=1.5Hz),
6.98-7.04 (2H, m), 7.19 (2H, s),
7.57 (1H, s).

By using a suitable starting material and by a method similar to that employed in Reference example
25 4, there was obtained a compound of Reference example 5 shown in Table 1 as follows.

Table 1 $R^3-(A)_n-R^{20}$

Reference

| <u>example No.</u> | <u>R²⁰</u> | <u>-(A)_n-</u> | <u>R³</u> | <u>Crystal form</u> |
|--------------------|-----------------------|--------------------------|--|---------------------|
| 5 | NH ₂ | -CH ₂ - |  | Brown solid |

5

Reference example 6

1.5 Grams of 5-nitroindole was dissolved in 70 ml of dimethylformamide, then 370 mg of sodium hydride (in oil) was added thereto, the mixture was stirred under nitrogen gas stream at 60°C for 1 hour. Under cooling at 0°C, 1.63 g of 5-chloromethyl-1-isopropyl-1,2,3,4-tetrazole was added, the reaction mixture was stirred at room temperature for 4.5 hours. After the reaction was finished, water was added to the reaction mixture, then the separated crystals were collected by filtration and washed with water. The crystals were dissolved in dichloromethane, the solution was dried with anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue obtained was subjected to a silica gel column chromatography (eluent: dichloromethane - 3% methanol/dichloromethane), there was obtained 2.3 g of 1-(1-isopropyl-1,2,3,4-tetrazol-5-ylmethyl)-5-nitroindole as in the form of yellow powder.

25

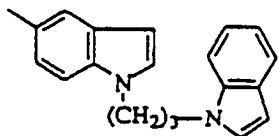
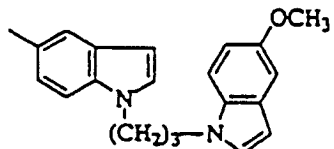
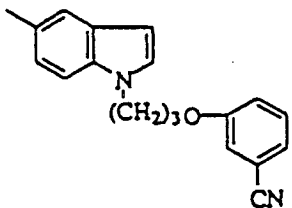
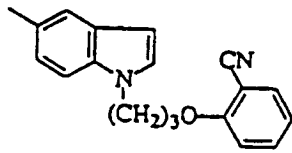
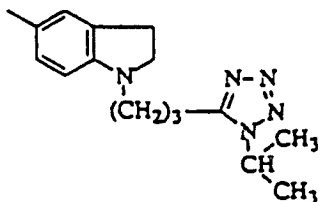
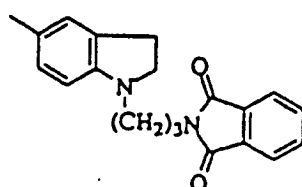
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¹H-NMR (250MHz, CDCl₃) δ ppm:

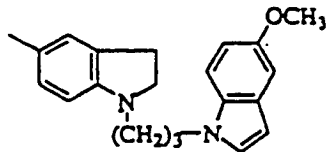
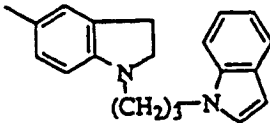
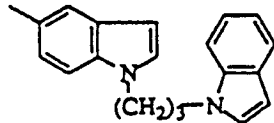
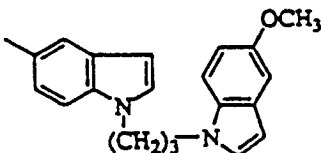
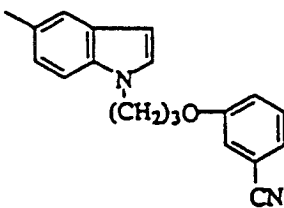
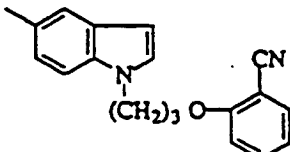
1.35 (6H, d, J=6.5Hz), 4.37-4.47 (1H, m),
5.70 (2H, s), 6.79-6.81 (1H, m),
7.27-7.30 (1H, m), 7.48 (1H, d, J=9Hz),
5 8.12-8.17 (1H, m), 8.59 (1H, d, J=2Hz).

By using suitable starting materials and by method similar to that employed in Reference example 6, there were obtained compounds of Reference examples 7 to 49 as shown in Tables 2 to 8 as follows.

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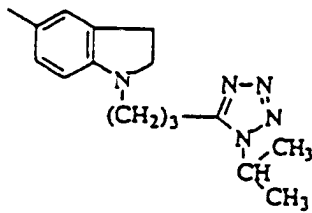
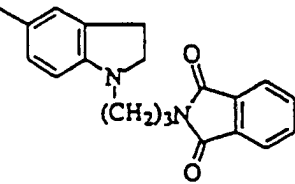
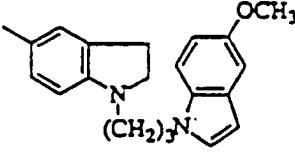
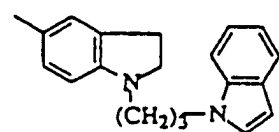
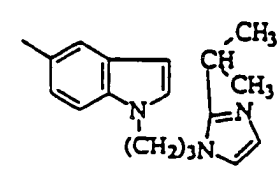
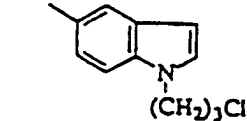
| Reference example No. | Table 2 | | R ³ - (A) n - R ²⁰ | Crystal form |
|--------------------------|-----------------|-----------|--|------------------------------|
| | R ²⁰ | - (A) n - | R ³ | |
| 7 | NO ₂ | - |  | Yellow powdery product |
| 8 | NO ₂ | - |  | Yellow powdery product |
| 9 | NO ₂ | - |  | Yellow powdery product |
| 10 | NO ₂ | - |  | Yellow powdery product |
| 11 | NO ₂ | - |  | Brown oily product |
| 12 | NO ₂ | - |  | Brown powdery product |

77

| Reference example No. | Table 3 | | $R^3 - (A)n - R^{20}$ | | Crystal form |
|--------------------------|---------------|----------|--|--|-----------------------------------|
| | R^{20} | $-(A)n-$ | R^3 | | |
| 13 | NO_2 | - |  | | Dark yellow powdery product |
| 14 | NO_2 | - |  | | Dark yellow powdery product |
| 15 | NH_2 | - |  | | |
| 16 | NH_2 | - |  | | Brown oily product |
| 17 | NH_2 | - |  | | Pale brown oily product |
| 18 | NH_2 | - |  | | Pale brown oily product |

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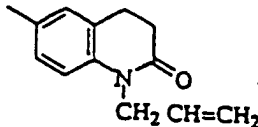
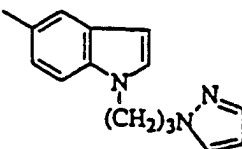
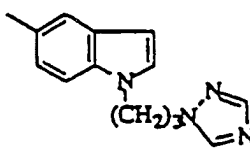
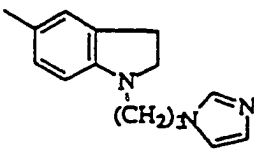
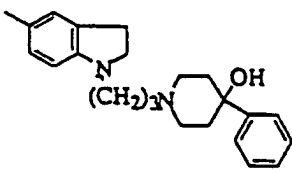
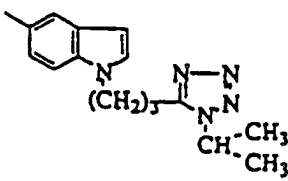
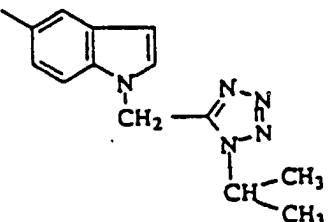
 $R^3 - (A) n - R^{20}$

| Reference example No. | Table 4 | R^{20} | $- (A) n -$ | R^3 | Crystal form |
|--------------------------|---------|----------|-------------|--|-----------------------------|
| 19 | | NH_2 | - |  | Black oily product |
| 20 | | NH_2 | - |  | Brown powdery product |
| 21 | | NH_2 | - |  | Dark violet oily product |
| 22 | | NH_2 | - |  | Dark violet oily product |
| 23 | | NH_2 | $-CH_2-$ |  | Yellow oily product |
| 24 | | CN | - |  | Pale yellow oily product |

79

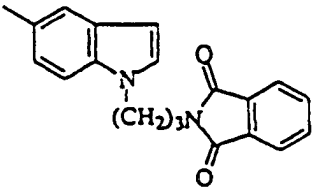
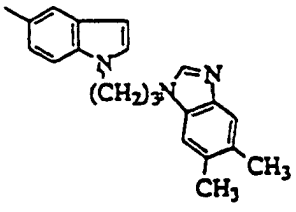
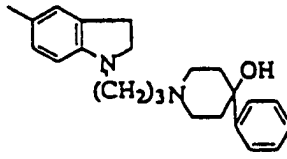
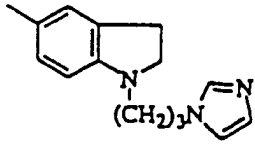
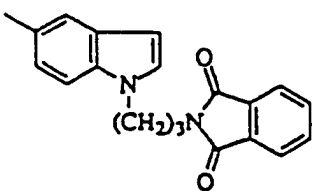
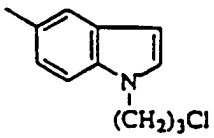
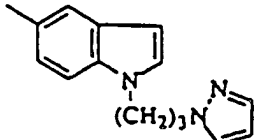
Table 5

 $R^3 - (A) n - R^{20}$

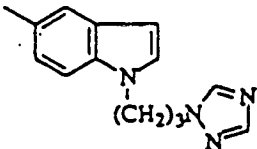
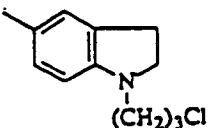
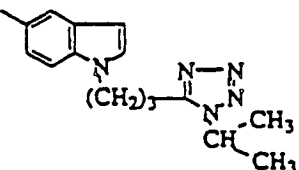
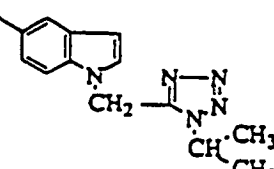
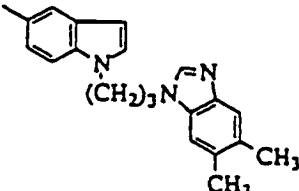
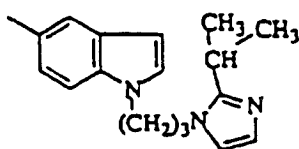
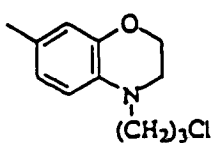
| Reference example No. | R^{20} | $- (A) n -$ | R^3 | Crystal form |
|--------------------------|----------|-------------|--|-----------------------|
| 25 | NH_2 | - |  | |
| 26 | NH_2 | - |  | Brown oily product |
| 27 | NH_2 | - |  | Oily product |
| 28 | NH_2 | - |  | Brown oily product |
| 29 | NH_2 | - |  | Black oily product |
| 30 | NH_2 | - |  | Brown oily product |
| 31 | NH_2 | - |  | Brown oily product |

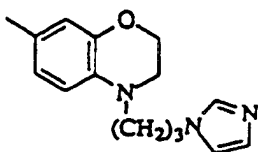
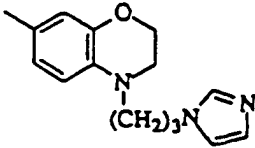
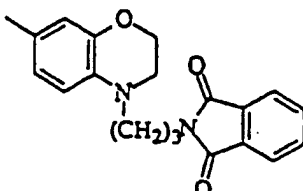
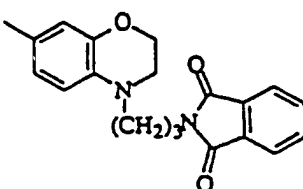
80

 $R^3 - (A) n - R^{20}$

| Reference example No. | Table 6 | | R^3 | Crystal form |
|--------------------------|----------|-------------|--|------------------------------|
| | R^{20} | $- (A) n -$ | | |
| 32 | NH_2 | - |  | Brown needle crystals |
| 33 | NH_2 | - |  | Brown oily product |
| 34 | NO_2 | - |  | Yellow powdery product |
| 35 | NO_2 | - |  | Yellow powdery product |
| 36 | NO_2 | - |  | Yellow powdery product |
| 37 | NO_2 | - |  | Yellow powdery product |
| 38 | NO_2 | - |  | Yellow powdery product |

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| Reference example No. | Table 7 | | $R^3 - (A) n - R^{20}$ | | Crystal form |
|--------------------------|---------------|-------------|--|--|------------------------------|
| | R^{20} | $- (A) n -$ | R^3 | | |
| 39 | NO_2 | - |  | | Yellow powdery product |
| 40 | NO_2 | - |  | | Yellow oily product |
| 41 | NO_2 | - |  | | Yellow oily product |
| 42 | NO_2 | - |  | | Yellow powdery product |
| 43 | NO_2 | - |  | | Yellow powdery product |
| 44 | CN | - |  | | Pale yellow oily product |
| 45 | NO_2 | - |  | | Brown powdery product |

| Reference example No. | Table 8 R ^{2 0} | - (A) n- | R ³ - (A) n-R ^{2 0} R ³ | Crystal form |
|--------------------------|-----------------------------|----------|---|-------------------------|
| 46 | NO ₂ | - |  | Yellow solid product |
| 47 | NH ₂ | - |  | Black oily product |
| 48 | NO ₂ | - |  | Yellow powdery product |
| 49 | NH ₂ | - |  | Dark brown oily product |

The NMR spectrum data of compounds obtained in the above-mentioned Reference examples are shown as follows.

Compound of Reference example 5

- 5 ¹H-NMR (250MHz, CDCl₃) δ ppm:
1.60 (2H, brs), 4.07 (2H, d, J=1Hz),
7.10-7.26 (3H, m), 7.36-7.39 (1H, m),
7.65-7.68 (1H, m) 8.12 (1H, brs).

Compound of Reference example 7

- 10 ¹H-NMR (250MHz, DMSO-d₆) δ ppm:
2.2-2.4 (2H, m), 4.20 (2H, t, J=7.5Hz), 4.29
(2H, t, J=7.5Hz), 6.44 (1H, d, J=3Hz), 6.77
(1H, d, J=3Hz), 7.0-7.2 (2H, m), 7.35-7.45
(2H, m), 7.5-7.75 (3H, m), 7.97-8.02 (1H, m),
15 8.58 (1H, d, J=2Hz).

Compound of Reference example 8

- 20 ¹H-NMR (250MHz, CDCl₃) δ ppm:
2.4-2.5 (2H, m), 3.86 (3H, s),
4.07-4.13 (4H, m), 6.47 (1H, t, J=2.5Hz),
6.69 (1H, d, J=3.5Hz), 6.83-6.88 (1H, m),
7.01 (1H, d, J=3Hz), 7.07-7.18 (4H, m),
8.06 (1H, dd, J=2.5Hz, 9Hz),
8.59 (1H, d, J=2.5Hz).

Compound of Reference example 9

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.2-2.3 (2H, m), 3.97 (2H, t, J=6Hz),
4.46 (2H, t, J=7Hz), 6.77 (1H, d, J=3Hz),
5 7.23-7.27 (1H, m), 7.37-7.51 (3H, m),
7.67-7.72 (2H, m), 7.98 (1H, dd, J=2Hz, 9Hz),
8.57 (1H, d, J=2Hz).

Compound of Reference example 10

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

10 2.25-2.35 (2H, m), 4.07 (2H, t, J=6Hz),
4.48 (2H, t, J=7Hz), 6.78 (1H, d, J=3Hz),
7.07-7.19 (2H, m), 7.61-7.78 (4H, m),
8.0 (1H, dd, J=2Hz, 9Hz),
8.58 (1H, d, J=2Hz).

15 Compound of Reference example 11

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.57 (6H, d, J=6.5Hz), 2.2-2.3 (2H, m),
2.89 (2H, t, J=7Hz), 3.08 (2H, t, J=9Hz),
3.44 (2H, t, J=7Hz), 3.67 (2H, t, J=9Hz),
20 4.4-4.6 (1H, m), 6.24 (1H, d, J=9Hz),
7.85-7.9 (1H, m), 7.99-8.03 (1H, m).

Compound of Reference example 12

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

1.9-2.0 (2H, m), 3.01 (2H, t, J=8.5Hz),
25 3.37 (2H, t, J=9Hz), 3.66 (4H, m),

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6.51 (1H, d, J=9Hz), 7.78-7.96 (6H, m).

Compound of Reference example 13

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.0-2.1 (2H, m), 3.02 (2H, t, J=8.5Hz),
5 3.25 (2H, t, J=7.5Hz), 3.62 (2H, t, J=8.5Hz),
3.74 (3H, s), 4.21 (2H, t, J=7Hz),
6.30-6.35 (2H, m), 6.73-6.78 (1H, m),
7.05 (1H, d, J=2.5Hz), 7.32 (1H, d, J=3Hz),
7.38 (1H, d, J=9Hz), 7.80 (1H, s),
10 7.90-7.95 (1H, m).

Compound of Reference example 14

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.0-2.1 (2H, m), 3.02 (2H, t, J=8.5Hz),
3.27 (2H, t, J=7.5Hz), 3.62 (2H, t, J=9Hz),
15 4.26 (2H, t, J=7Hz), 6.34 (1H, d, J=9Hz),
6.44-6.45 (1H, m), 6.98-7.15 (2H, m),
7.38 (1H, d, J=3Hz), 7.48-7.56 (2H, m),
7.80 (1H, d, J=2.5Hz), 7.93 (1H, dd,
J=2.5Hz, 9Hz).

20 Compound of Reference example 15

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.35-2.45 (2H, m), 4.00-4.11 (4H, m),
6.33-6.34 (1H, m), 6.52 (1H, d, J=3Hz),
6.64-6.68 (1H, m), 6.94-7.22 (7H, m),
25 7.64 (1H, d, J=7.5Hz).

Compound of Reference example 16

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.35-2.45 (2H, m), 3.85 (3H, s),
3.99-4.07 (4H, m), 6.33 (1H, d, J=3Hz),
5 6.43 (1H, d, J=3Hz), 6.64-6.68 (1H, m),
6.83-6.88 (1H, m), 6.94-6.97 (2H, m),
7.01-7.04 (2H, m), 7.10-7.13 (2H, m).

Compound of Reference example 17

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 2.25-2.35 (2H, m), 3.4-3.6 (2H, br),
3.85 (2H, t, J=6Hz), 4.30 (2H, t, J=6.5Hz),
6.28-6.30 (1H, m), 6.62-6.66 (1H, m),
6.92-6.97 (2H, m), 7.0-7.15 (3H, m),
7.23-7.26 (1H, m), 7.33-7.39 (1H, m)

15 Compound of Reference example 18

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.3-2.4 (2H, m), 3.3-3.7 (2H, br),
3.89 (2H, t, J=8Hz), 4.38 (2H, t, J=8Hz),
6.26 (1H, d, J=3Hz), 6.6-6.7 (1H, m),
20 6.75-6.81 (1H, m), 6.91 (1H, s),
7.0-7.1 (2H, m), 7.17-7.20 (1H, m),
7.4-7.5 (1H, m), 7.58 (1H, d, J=8Hz).

Compound of Reference example 19

¹H-NMR (250MHz, CDCl₃) δ ppm:

25 1.55 (6H, d, J=6.5Hz), 2.1-2.25 (2H, m),

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2.8-3.4 (8H, m), 4.51-4.62 (1H, m),
6.2-6.6 (3H, m)

Compound of Reference example 20

¹H-NMR (250MHz, CDCl₃) δ ppm:

5 1.92-2.04 (2H, m), 2.6-3.5 (8H, brm),
 3.83 (2H, t, J=7Hz), 6.3-6.6 (3H, m),
 7.67-7.86 (4H, m).

Compound of Reference example 21

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 2.0-2.2 (2H, m), 2.8-3.0 (4H, m),
 3.19 (2H, t, J=8Hz), 3.86 (3H, s),
 4.25 (2H, t, J=6.5Hz), 6.2-6.3 (1H, m),
 6.4-6.5 (2H, m), 6.57 (1H, s),
 6.84-6.88 (1H, m), 7.08-7.11 (2H, m),
15 7.26 (1H, t, J=5Hz).

Compound of Reference example 22

¹H-NMR (250MHz, CDCl₃) δ ppm:

 2.1-2.2 (2H, m), 2.8-3.0 (4H, m),
 3.20 (2H, t, J=8Hz), 4.29 (2H, t, J=7Hz),
20 6.2-6.3 (1H, m), 6.4-6.6 (3H, m),
 7.1-7.3 (3H, m), 7.38 (1H, d, J=8Hz),
 7.64 (1H, d, J=7.5Hz).

Compound of Reference example 23

¹H-NMR (250MHz, CDCl₃) δ ppm:

5 1.22 (6H, d, J=7Hz), 2.3-2.4 (2H, m), 2.7-2.8
(2H, m), 3.81 (2H, t, J=7.5Hz), 3.95 (2H, s),
4.16 (2H, t, J=7Hz), 6.51 (1H, d, J=3Hz),
6.77 (1H, d, J=1.5Hz), 6.98-7.04 (2H, m),
7.19 (2H, s), 7.57 (1H, s).

Compound of Reference example 24

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 2.23-2.33 (2H, m), 3.45 (2H, t, J=6Hz),
4.38 (2H, t, J=6.5Hz), 6.60 (1H, d, J=3.5Hz),
7.2 (1H, s), 7.44 (2H, d, J=1Hz),
7.98 (1H, t, J=1Hz).

Compound of Reference example 25

15 ¹H-NMR (250MHz, CDCl₃) δ ppm:

2.6-2.7 (2H, m), 2.8-2.9 (2H, m),
3.55 (2H, brs), 4.4-4.6 (2H, m),
5.1-5.3 (2H, m), 5.8-6.0 (1H, m),
6.5-6.6 (2H, m), 6.8-6.9 (1H, m).

20 Compound of Reference example 26

¹H-NMR (250MHz, CDCl₃) δ ppm:

25 2.36-2.46 (2H, m), 3.3-3.7 (2H, br),
4.0-4.1 (4H, m), 6.2-6.4 (2H, m),
6.6-6.7 (1H, m), 6.93 (1H, d, J=2Hz),
7.0-7.1 (2H, m), 7.30 (1H, d, J=2Hz),

7.56 (1H, d, J=1.5Hz).

Compound of Reference example 27

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.4-2.6 (2H, m), 3.1-3.8 (2H, br),
5 4.1-4.3 (4H, m), 6.33 (1H, d, J=3Hz),
6.68 (1H, dd, J=8.5Hz, 2Hz), 6.9-7.1 (3H, m),
7.97 (2H, d, J=12Hz).

Compound of Reference example 28

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 2.0-2.1 (2H, m), 2.85-2.9 (4H, m),
3.19 (2H, t, J=9Hz), 4.11 (2H, t, J=7Hz),
6.25 (1H, d, J=8Hz), 6.45-6.5 (1H, m),
6.5-6.6 (1H, m), 6.93 (1H, s), 7.08 (1H, s),
7.49 (1H, s).

15 Compound of Reference example 29

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.7-2.0 (4H, m), 2.2-2.4 (2H, m),
2.5-2.7 (4H, m), 2.9-3.0 (4H, m),
3.01 (2H, t, J=7Hz), 3.24 (2H, t, J=8Hz),
20 6.37 (1H, d, J=8Hz), 6.4-6.5 (1H, m),
6.56 (1H, s), 7.3-7.4 (3H, m),
7.52 (2H, d, J=7Hz).

Compound of Reference example 30

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.43 (6H, d, J=6.5Hz), 2.4-2.5 (2H, m),
2.59 (2H, t, J=8Hz), 4.1-4.2 (1H, m),
5 4.29 (2H, t, J=6.5), 6.3 (1H, d, J=2.5Hz),
6.62-6.66 (1H, m), 6.92-7.03 (3H, m).

Compound of Reference example 31

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.25 (6H, d, J=6.5Hz), 4.2-4.3 (1H, m),
10 5.57 (2H, s), 6.4 (1H, d, J=3Hz),
6.64-6.69 (1H, m), 6.9 (1H, d, J=2Hz),
6.99 (1H, d, J=3Hz), 7.1 (1H, d, J=8.5Hz).

Compound of Reference example 32

¹H-NMR (250MHz, CDCl₃) δ ppm:

15 2.16-2.28 (2H, m), 3.73 (2H, t, J=7Hz),
4.12 (2H, t, J=7Hz), 6.28 (1H, d, J=3Hz),
6.64-6.69 (1H, m), 6.9 (1H, d, J=2Hz),
7.11-7.14 (2H, m), 7.7-7.73 (2H, m),
7.82-7.86 (2H, m).

20 Compound of Reference example 33

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.35-2.5 (8H, m), 4.0-4.1 (4H, m),
6.35 (1H, d, J=2.5Hz), 6.67-6.70 (1H, m),
6.96-7.06 (4H, m), 7.57 (1H, s),
25 7.70 (1H, s).

Compound of Reference example 34

¹H-NMR (250MHz, CDCl₃) δ ppm:

- 1.5-1.7 (1H, br), 1.76-1.87 (4H, m),
2.1-2.2 (2H, m), 2.43-2.5 (4H, m),
5 2.7-2.8 (2H, m), 3.08 (2H, t, J=8.5Hz),
3.33 (2H, t, J=7Hz), 3.68 (2H, t, J=8.5Hz),
6.32 (1H, d, J=9Hz), 7.2-7.4 (3H, m),
7.52 (2H, d, J=7Hz), 7.88 (1H, s),
8.02-8.06 (1H, m).

10 Compound of Reference example 35

¹H-NMR (250MHz, CDCl₃) δ ppm:

- 2.1-2.18 (2H, m), 3.09 (2H, t, J=8.5Hz),
3.20 (2H, t, J=7Hz), 3.59 (2H, t, J=8.5Hz),
4.07 (2H, t, J=7Hz), 6.17 (1H, d, J=9Hz),
15 6.92 (1H, t, J=1.5Hz), 7.12 (1H, s),
7.48 (1H, s), 7.91 (1H, s),
8.02-8.06 (1H, m).

Compound of Reference example 36

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

- 20 2.1-2.2 (2H, m), 3.61 (2H, t, J=7Hz),
4.36 (2H, t, J=7Hz), 6.75 (1H, d, J=2.5Hz),
7.71-7.76 (2H, m), 7.8-7.9 (4H, m),
7.99-8.04 (1H, m), 8.55 (1H, d, J=2Hz).

Compound of Reference example 37

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.18-2.29 (2H, m), 3.57 (2H, t, J=6.5Hz),
4.40 (2H, t, J=7Hz), 6.78 (1H, d, J=3Hz),
5 7.62-7.73 (2H, m), 8.02-8.06 (1H, m),
8.57 (1H, d, J=2Hz).

Compound of Reference example 38

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.40-2.51 (2H, m), 4.11 (2H, t, J=6.5Hz),
10 4.19 (2H, t, J=7Hz), 6.31 (1H, t, J=2Hz),
6.69-6.71 (1H, m), 7.24-7.34 (3H, m),
7.59 (1H, d, J=1.5Hz), 8.08-8.13 (1H, m),
8.59 (1H, d, J=2Hz).

Compound of Reference example 39

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.2-2.4 (2H, m), 4.19 (2H, t, J=7Hz),
15 4.32 (2H, t, J=7Hz), 6.77 (1H, d, J=3Hz),
7.65-7.68 (2H, m), 7.99-8.06 (2H, m),
8.50 (1H, s), 8.58 (1H, d, J=2Hz).

20 Compound of Reference example 40

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.0-2.1 (2H, m), 3.09 (2H, t, J=8Hz),
3.4-3.5 (2H, m), 3.6-3.7 (4H, m),
6.33-6.38 (1H, m), 7.89 (1H, s),
25 8.03-8.08 (1H, m).

Compound of Reference example 41

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.5 (6H, d, J=6.5Hz), 2.4-2.6 (2H, m),
2.68 (2H, t, J=6.5Hz), 4.3-4.4 (1H, m),
5 4.47 (2H, t, J=6.5Hz), 6.71 (1H, d, J=3Hz),
7.2-7.3 (2H, m), 8.0-8.1 (1H, m),
8.59 (1H, d, J=2Hz).

Compound of Reference example 42

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 1.35 (6H, d, J=6.5Hz), 4.37-4.47 (1H, m),
5.70 (2H, s), 6.79-6.81 (1H, m),
7.27-7.30 (1H, m), 7.48 (1H, d, J=9Hz),
8.12-8.17 (1H, m), 8.59 (1H, d, J=2Hz).

Compound of Reference example 43

¹H-NMR (250MHz, CDCl₃) δ ppm:

15 2.33 (3H, s), 2.37 (3H, s),
2.45-2.56 (2H, m), 4.09-4.20 (4H, m),
6.74 (1H, d, J=3Hz), 6.94 (1H, s),
7.15-7.21 (2H, m), 7.58 (1H, s),
20 7.72 (1H, s), 8.05-8.09 (1H, m),
8.60 (1H, d, J=2Hz).

Compound of Reference example 44

¹H-NMR (250MHz, CDCl₃) δ ppm:

25 1.22 (6H, d, J=7Hz), 2.3-2.4 (2H, m),
2.6-2.8 (1H, m), 3.84 (2H, t, J=7Hz),

4.19 (2H, t, J=7Hz), 6.63 (1H, d, J=3Hz),
6.78 (1H, d, J=1.5Hz), 7.01 (1H, d, J=1.5Hz),
7.16 (1H, d, J=3.5Hz), 7.2-7.3 (1H, m),
7.4-7.5 (1H, m), 8.0 (1H, s).

5 Compound of Reference example 45

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.1-2.2 (2H, m), 3.5-3.7 (6H, m),
4.2-4.3 (2H, m), 6.63 (1H, d, J=9Hz),
7.67 (1H, d, J=2.5Hz), 7.78-7.87 (1H, m).

10 Compound of Reference example 46

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.1-2.2 (2H, m), 3.3-3.4 (4H, m),
4.06 (2H, t, J=6.5Hz), 4.23 (2H, t, J=4.5Hz),
6.42 (1H, d, J=9Hz), 6.95 (1H, s),
7.13 (1H, s), 7.50 (1H, s), 7.67 (1H, d,
J=2.5Hz), 7.78 (1H, d, J=2.5Hz, 9Hz).

15

Compound of Reference example 47

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.0-2.1 (2H, m), 3.1-3.2 (4H, m),
4.04 (2H, t, J=7Hz), 4.22 (2H, t, J=4.5Hz),
6.2-6.3 (2H, m), 6.35-6.45 (1H, m),
6.93 (1H, s), 7.09 (1H, s), 7.49 (1H, s).

20

Compound of Reference example 48

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.0-2.1 (2H, m), 3.4-3.5 (4H, m),
3.78 (2H, t, J=7Hz), 4.25 (2H, t, J=4.5Hz),
5 6.56 (1H, d, J=9Hz), 7.64 (1H, d, J=2.5Hz),
7.73-7.88 (5H, m).

Compound of Reference example 49

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.95-2.04 (2H, m), 3.17-3.23 (4H, m),
10 3.77 (2H, t, J=7Hz), 4.22 (2H, t, J=4.5Hz),
6.2-6.24 (2H, m), 6.5-6.55 (1H, m),
7.7-7.74 (2H, m), 7.83-8.02 (2H, m).

Reference example 50

To 926 mg of 5-methoxyindole was added 30 ml
15 of dimethylformamide and 230 mg of sodium hydride (in
oil), this mixture was stirred under nitrogen gas
stream at 60°C for 1 hour. Then 1.5 g of 1-(3-chloro-
propyl)-5-nitroindole was added to the reaction mixture
and stirred at room temperature overnight. The
20 reaction mixture was further stirred at 60°C for 5.5
hours, then water was added thereto, and the crystals
being separated were collected by filtration, and
washed with water. The washed crystals were subjected
to a silica gel column chromatography (eluent:
25 dichloromethane), there was obtained 1.8 g of 1-[3-(5-
methoxyindol-1-yl)propyl]-5-nitroindole as in the

form of yellow powdery product.

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.4-2.5 (2H, m), 3.86 (3H, s),

4.07-4.13 (4H, m), 6.47 (1H, t, J=2.5Hz),

5 6.69 (1H, d, J=3.5Hz), 6.83-6.88 (1H, m),

7.01 (1H, d, J=3Hz), 7.07-7.18 (4H, m),

8.06 (1H, dd, J=2.5Hz, J=9Hz),

8.59 (1H, d, J=2.5Hz).

10 By using suitable starting materials, and by
a method similar to that employed in Reference example
50, there were obtained compounds of the above-
mentioned Reference examples 7, 9, 10, 12-18, 20-23,
26-29, 32-36, 38, 39, 43, 44 and 46-49.

15

Reference example 51

To 500 ml of ethanol solution containing 26 g
of 2-benzylamino-4-chloroaniline was added 45.7 g of
polymer form (45-50% toluene solution) of ethyl
20 glyoxylate, further 28.4 g of iodine was added and the
reaction mixture was stirred at room temperature for 20
minutes. Then 27.8 g of sodium thiosulfate aqueous
solution was added thereto, the crystals being
separated were collected by filtration, and washed with
25 water and ethanol, then dried. There was obtained 26.1
g of ethyl 1-benzyl-6-chlorobenzimidazol-2-carboxylate
as in the form of pale brown powdery product.

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.45 (3H, t, J=7Hz), 4.49 (2H, q, J=7Hz),
5.85 (2H, s), 7.1-7.5 (7H, m),
7.85 (1H, d, J=8.5Hz).

5

By using a suitable starting material, and by a method similar to that employed in Reference example 51, compound of the above-mentioned Reference example 2 was obtained.

10

Example 1A

A mixture of 2.2 g of methyl 1-benzyl-6-chlorobenzimidazol-2-carboxylate and 5.3 g of 1-[3-(2-isopropylimidazol-1-yl)propyl]-5-aminomethylindole was stirred at 80°C for 1.5 hours, after confirmed that the starting materials were disappeared, the reaction mixture was dissolved in chloroform, then washed with water and an aqueous solution saturated with sodium chloride, and dried with anhydrous magnesium sulfate, then the solvent was removed by distillation under reduced pressure. The resulting residue was subjected a silica gel column chromatography (eluent: 3% methanol/dichloromethane), then fumaric acid was added and recrystallized from diisopropyl ether-ethanol, there was obtained 4 g of 1-benzyl-6-chloro-2-{1-[3-(2-isopropylimidazol-1-yl)propyl]indol-5-ylmethylaminocarbonyl}benzimidazole•fumarate as in the form of pale yellow powdary product.

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

1.10 (6H, d, J=7Hz), 2.1-2.3 (2H, m),
2.8-2.95 (1H, m), 3.88 (2H, t, J=7.5Hz),
4.20 (2H, t, J=7Hz), 4.55 (2H, d, J=6.5Hz),
5.98 (2H, s), 6.43 (1H, d, J=3Hz),
6.62 (2H, s), 6.66 (1H, d, J=1.5Hz),
7.10 (1H, d, J=1.5Hz), 7.15-7.38 (10H, m),
7.53 (1H, s), 7.77 (1H, d, J=8.5Hz),
7.84 (1H, d, J=1.5Hz), 9.57 (1H, t, J=4Hz)

10 Example 1B

130 Milligrams of lithium aluminum hydride was suspended in 70 ml of tetrahydrofuran, then 2.2 g of 6-amino-3,4-dihydro-2(1H)-quinolinone was added gradually thereto, and the mixture was stirred at room temperature overnight. The reaction mixture was further stirred for 2 hours under refluxing condition, then 1 g of methyl 1-benzyl-6-chlorobenzimidazol-2-carboxylate was added, the reaction was continued by refluxing for 3 hours. After the reaction was finished, then water and 10% aqueous solution of potassium hydroxide were added, the reaction mixture was diluted with ethyl acetate and filtered with Celite, and the filtrate was washed with chloroform, the solvent was removed by distillation under reduced pressure. To the residue thus obtained was added ethanol and heated, the insoluble matters were collected by filtration and recrystallized from

dimethylformamide, there was obtained 0.11 g of 1-benzyl-6-chloro-2-(3,4-dihydro-2(1H)-quinolinon-6-ylaminocarbonyl)benzimidazole as in the form of yellow powdery product.

5 Melting point: Higher than 290°C

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.44 (2H, t, J=7Hz), 2.87 (1H, t, J=7Hz),

5.99 (2H, s), 6.83 (1H, d, J=9Hz),

7.21-7.40 (6H, m), 7.57-7.6 (1H, m),

10 7.72 (1H, s), 7.86-7.88 (2H, m),

10.08 (1H, s).

Example 1C

To 2.2 g of 5-amino-1-[3-(1-isopropyl-5-tetrazolyl)propyl]indole was added 40 ml of toluene,
15 then this mixture was stirred under nitrogen gas atmosphere by cooling in a methanol-ice bath. To this reaction mixture was added 4 ml of n-hexane solution of 2M trimethylaluminum dropwise from syringe, then reaction mixture was stirred for 20 minutes, and
20 further stirred at room temperature for 1 hour. 2.18 Grams of methyl 1-benzyl-6-chlorobenzimidazol-2-carboxylate was added to the reaction mixture and was stirred for 5 to 6 hours under refluxing condition. Next, 10% hydrochloric acid was added, and the crystals
25 being separated were collected by filtration. Water-chloroform was added to the crystals, this solution was made alkaline with 10% aqueous solution of potassium

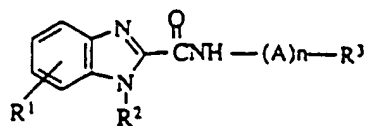
hydroxide, then was filtered with Celite, the chloroform layer was washed with water, an aqueous solution saturated with sodium chloride. The chloroform layer was dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue thus obtained was subjected to a silica gel column chromatography (eluent: 3% methanol/dichloromethane), and recrystallized from ethyl acetate-n-hexane, there was obtained 2.27 g of 1-benzyl-6-chloro-2-{1-[3-(1-isopropyltetrazol-5-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole as in the form of yellow needle crystals.

Melting point: 190-191°C.

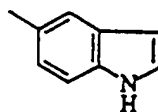
By using suitable starting materials, and by methods similar to those employed in Examples 1A to 1C, there were obtained compounds of Examples 2 to 50 as shown in Tables 9 to 33 as follows.

101

Table 9



Example 2

Structure R³ :R¹ : 6-ClR² : -(A)_n : —

Crystal form : Brown granules

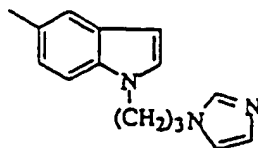
Recrystallization

solvent: Ethyl acetate

Melting point : 205 - 207℃

Form of compound : Free form

Example 3

Structure R³ :R¹ : 6-ClR² : -(A)_n : —

Crystal form : Pale yellow needles

Recrystallization

solvent: Methanol

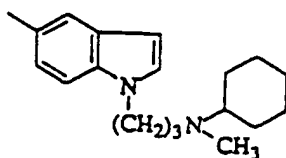
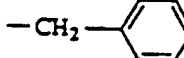
Melting point : 187 - 188℃

Form of compound : Free form

Table 10

Example 4

Structure

 R^3 : R^1 : 6-Cl R^2 :  $-(A)_n-$: 

Crystal form : Pale yellow needles

Recrystallization

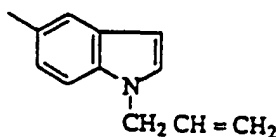
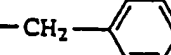
solvent: Ethanol

Melting point : 129-130 $^{\circ}$

Form of compound : Free form

Example 5

Structure

 R^3 : R^1 : 6-Cl R^2 :  $-(A)_n-$: 

Crystal form : Colorless needles

Recrystallization

solvent: Ethyl acetate-ethanol

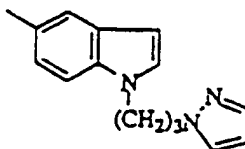
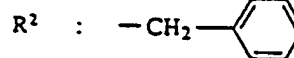
Melting point : 154-155 $^{\circ}$

Form of compound : Free form

Table 11

Example 6

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale yellow needles

Recrystallization

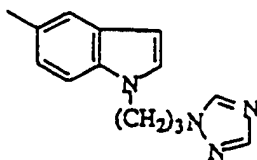
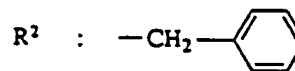
solvent: Chloroform-ethyl acetate

Melting point : 165-166°

Form of compound : Free form

Example 7

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

solvent: Methanol-ethyl acetate

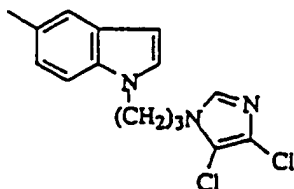
Melting point : 196-197°

Form of compound : Free form

Table 12

Example 8

Structure

R³ :R¹ : 6-ClR² : —(A)_n— : —

Crystal form : Brown granules

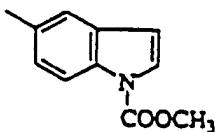
Recrystallization

solvent: Ethyl acetate-n-hexaneMelting point : 191-192^o

Form of compound : Free form

Example 9

Structure

R³ :R¹ : 6-ClR² : —(A)_n— : —

Crystal form : Pale brown powdery

Recrystallization

solvent: Ethyl acetate-diisopropyl ether

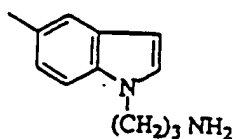
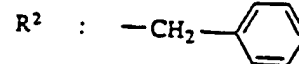
Melting point : 194-195^o

Form of compound: Free form

Table 13

Example 10

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow granules

Recrystallization

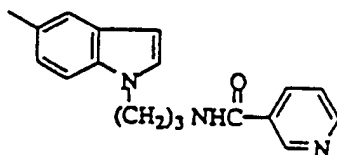
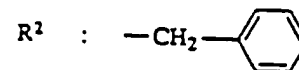
solvent: Ethyl acetate-n-hexane

Melting point : 106-108℃

Form of compound : Free form

Example 11

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

solvent: Chloroform

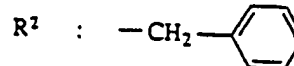
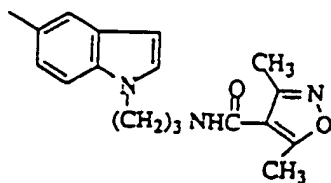
Melting point : 206-207℃

Form of compound : Free form

Table 14

Example 12

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

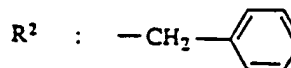
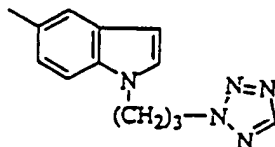
solvent: Dimethylformamide-water

Melting point : 217-218℃

Form of compound : Free form

Example 13

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale yellow needles

Recrystallization

solvent: Dichloromethane-n-hexane

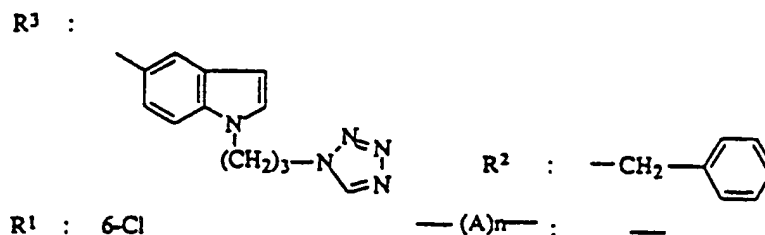
Melting point : 146-147℃

Form of compound : Free form

Table 15

Example 14

Structure



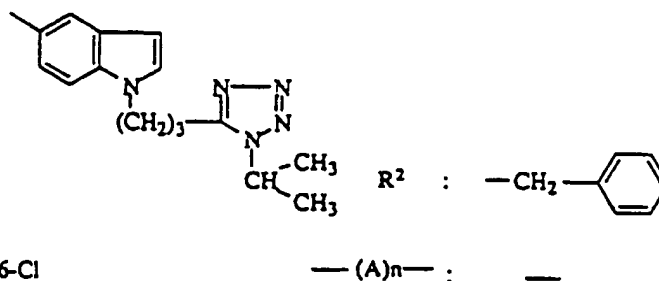
Crystal form : Colorless needles

Recrystallization

solvent: Ethyl acetate-n-hexaneMelting point : 178-179 \uparrow

Form of compound : Free form

Example 15

Structure R^3 :

Crystal form : Yellow needles

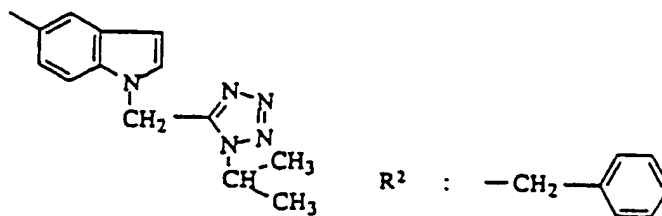
Recrystallization

solvent: Ethyl acetate-n-hexaneMelting point : 190-191 \uparrow

Form of compound : Free form

Table 16

Example 16

Structure R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale yellow needles

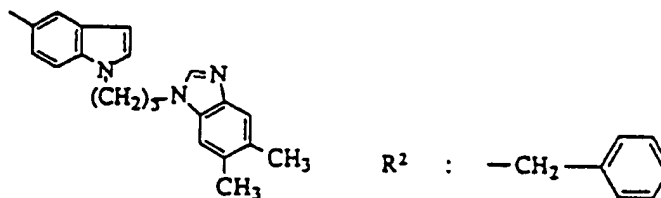
Recrystallization

solvent: Ethyl acetate

Melting point : 229-231 \uparrow . (decomposed)

Form of compound : Free form

Example 17

Structure R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale yellow powdery

Recrystallization

solvent: Ethyl acetate

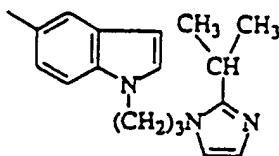
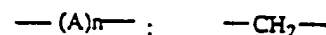
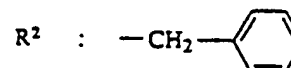
Melting point : 197-198 \uparrow .

Form of compound : Free form

Table 17

Example 18

Structure

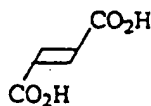
R³ :R¹ : 6-Cl

Crystal form : Pale yellow powdery

Recrystallization

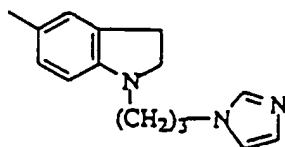
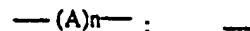
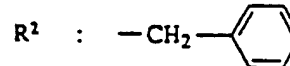
solvent: Ethanol-diisopropyl ether

Form of compound :



Example 19

Structure

R³ :R¹ : 6-Cl

Crystal form : Yellow powdery

Recrystallization

solvent: Methanol-diisopropyl ether

Melting point : 189-190℃.

Form of compound :

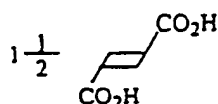
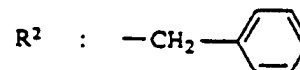
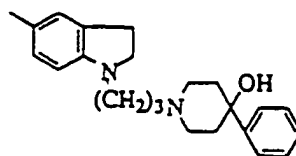


Table 18

Example 20

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

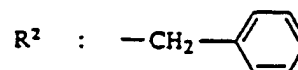
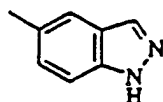
solvent: Chloroform

Melting point : 186-187℃

Form of compound : Free form

Example 21

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale brown powdery

Recrystallization

solvent: Ethanol-ethyl acetate

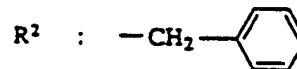
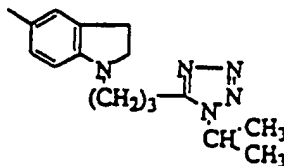
Melting point : 277℃.

Form of compound : Free form

Table 19

Example 22

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

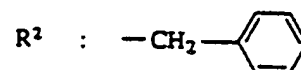
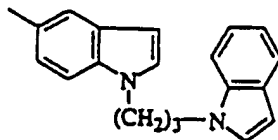
solvent: Ethyl acetate-ethanol

Melting point : 155-156^o

Form of compound : Free form

Example 23

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : White powdery

Recrystallization

solvent: Ethyl acetate

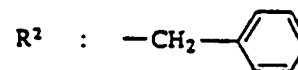
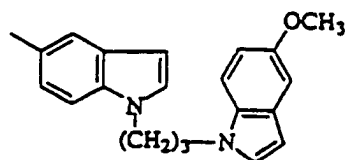
Melting point : 160-161^o.

Form of compound : Free form

Table 20

Example 24

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow powdery

Recrystallization

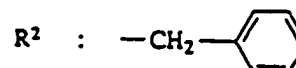
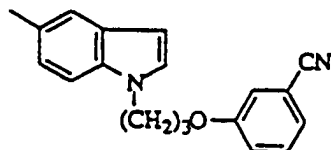
solvent: Ethyl acetate-dichloromethane

Melting point : 169-170°C

Form of compound : Free form

Example 25

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale yellow powdery

Recrystallization

solvent: Ethyl acetate-n-hexane

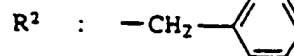
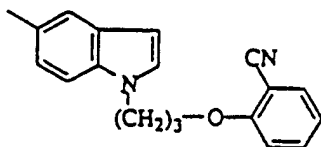
Melting point : 166-167°C.

Form of compound : Free form

Table 21

Example 26

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Pale brown needles

Recrystallization

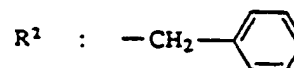
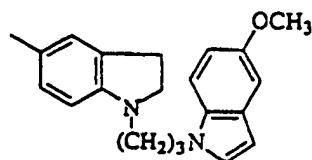
solvent: Ethyl acetate-n-hexane

Melting point : 156℃

Form of compound : Free form

Example 27

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Bright yellow needles

Recrystallization

solvent: Ethyl acetate-n-hexane

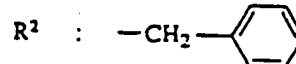
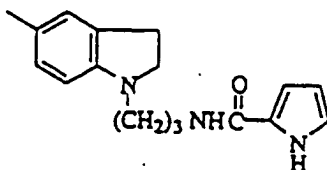
Melting point : 157℃.

Form of compound : Free form

Table 22

Example 28

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow granules

Recrystallization

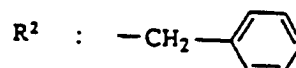
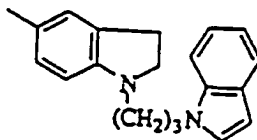
solvent: Dimethylformamide-water

Melting point : 213-221°

Form of compound : Free form

Example 29

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Bright yellow needles

Recrystallization

solvent: Ethyl acetate-n-hexane

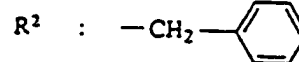
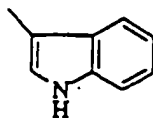
Melting point : 136-137°C.

Form of compound : Free form

Table 23

Example 30

Structure

 R^3 : R^1 : 6-Cl

Crystal form : Colorless granules

Recrystallization

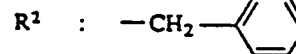
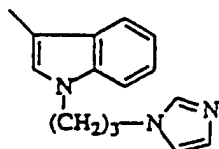
solvent: Ethyl acetate

Melting point : 187-188 $^{\circ}$

Form of compound : Free form

Example 31

Structure

 R^3 : R^1 : 6-Cl

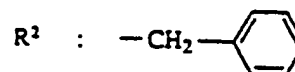
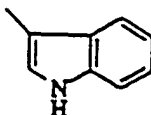
Crystal form : White amorphous

Form of compound : Hydrochloride

Table 24

Example 32

Structure

R³ :R¹ : 6-Cl

Crystal form : Colorless needles

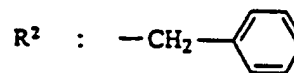
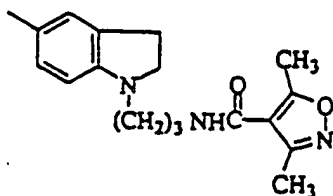
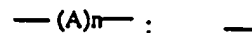
Recrystallization

solvent: Ethyl acetate-n-hexane

Melting point : 173-174°

Form of compound : Free form

Example 33

Structure R³ :R¹ : 6-Cl

Crystal form : Yellow powdery

Recrystallization

solvent: Ethanol-n-hexane

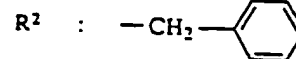
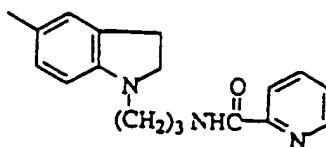
Melting point : 153-155°.

Form of compound : Free form

Table 25

Example 34

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow needles

Recrystallization

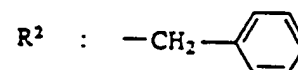
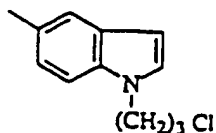
solvent: Ethyl acetate

Melting point : 139-140°

Form of compound : Free form

Example 35

Structure

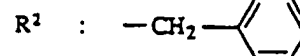
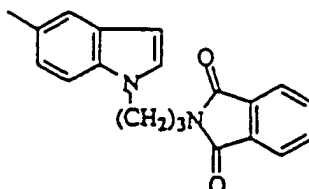
R³ :R¹ : 6-Cl—(A)_n— : —

Form of compound : Free form

Table 26

Example 36

Structure

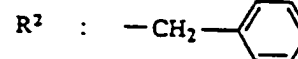
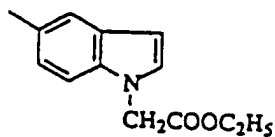
 R^3 : R^1 : 6-Cl $-(A)_n-$: $-$

Crystal form : Yellow needles

Form of compound : Free form

Example 37

Structure

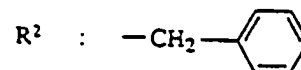
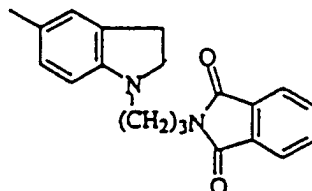
 R^3 : R^1 : 6-Cl $-(A)_n-$: $-$

Form of compound : Free form

Table 27

Example 38

Structure

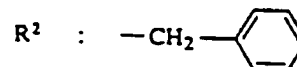
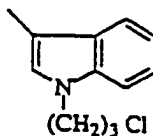
 R^3 : R^1 : 6-Cl $-(A)_n-$: $-$

Crystal form : Brown solid

Form of compound : Free form

Example 39

Structure

 R^3 : R^1 : 6-Cl $-(A)_n-$: $-(\text{CH}_2)_2-$

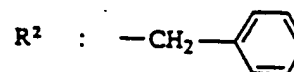
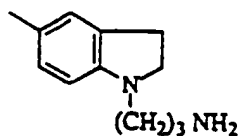
Crystal form : Pale yellow oily

Form of compound : Free form

Table 28

Example 40

Structure

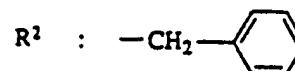
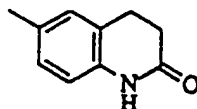
 $R^3 :$  $R^1 : 6-Cl$ $-(A)_n-$: —

Crystal form : Yellow powdery

Form of compound : Free form

Example 41

Structure

 $R^3 :$  $R^1 : 6-Cl$ $-(A)_n-$: —

Crystal form : Yellow powdery

Recrystallization

solvent: Dimethylformamide

Melting point : Higher than 290℃

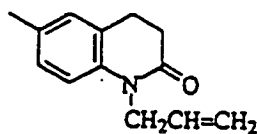
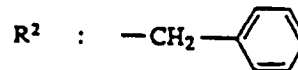
Form of compound : Free form

121

Table 29

Example 42

Structure

R³ :R¹ : 6-ClR² :—(A)_n— : —

Crystal form : Yellow powdery

Recrystallization

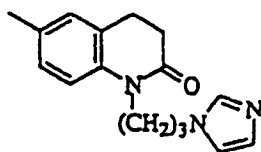
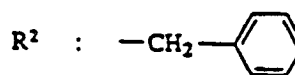
solvent: Ethyl acetate-n-hexane

Melting point : 183-184℃

Form of compound : Free form

Example 43

Structure

R³ :R¹ : 6-ClR² :—(A)_n— : —

Crystal form : Pale yellow powdery

Recrystallization

solvent: Ethyl acetate

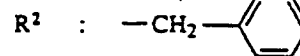
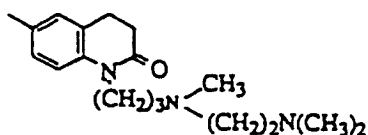
Melting point : 195℃

Form of compound : Free form

Table 30

Example 44

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

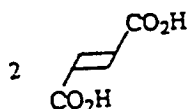
Crystal form : Yellow powdery

Recrystallization

solvent: Ethanol

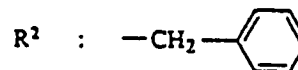
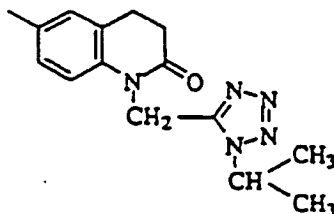
Melting point : 200-202 \uparrow

Form of compound :



Example 45

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Colorless needles

Recrystallization

solvent: Ethyl acetate-ethanol

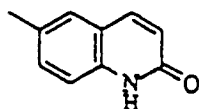
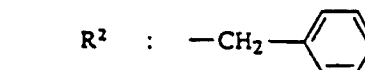
Melting point : 227-228 \uparrow

Form of compound : Free form

Table 31

Example 46

Structure

R³ :R¹ : 6-ClR² :—(A)_n— : —

Crystal form : Pale brown powdery

Recrystallization

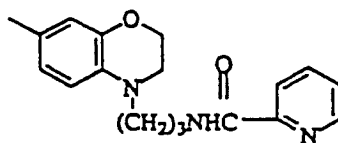
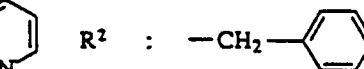
solvent: Chloroform-isopropyl alcohol

Melting point : Higher than 290℃

Form of compound : Free form

Example 47

Structure

R³ :R¹ : 6-ClR² :—(A)_n— : —

Crystal form : Bright yellow needles

Recrystallization

solvent: Ethyl acetate-diisopropyl ether

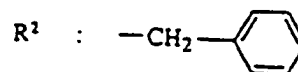
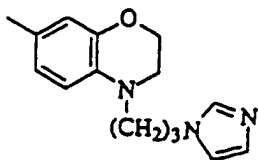
Melting point : 146-148℃

Form of compound : Free form

Table 32

Example 48

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow powdery

Recrystallization

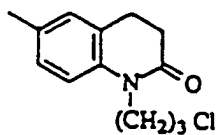
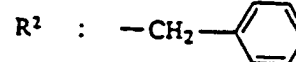
solvent: Ethyl acetate-n-hexane

Melting point : 175-176°

Form of compound : Free form

Example 49

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

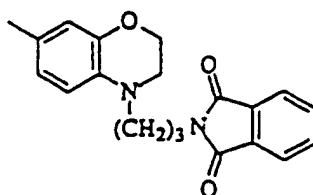
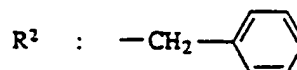
Form of compound : Free form

125

Table 33

Example 50

Structure

R³ :R¹ : 6-Cl—(A)_n— : —

Crystal form : Yellow amorphous

5 Form of compound : Free form

10 The NMR spectrum data of compounds obtained
in the above-mentioned Examples are shown as follow.

Compound of Example 18

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

1.10 (6H, d, J=7Hz), 2.1-2.3 (2H, m),
2.8-2.95 (1H, m), 3.88 (2H, t, J=7.5Hz),
15 4.20 (2H, t, J=7Hz), 4.55 (2H, d, J=6.5Hz),
5.98 (2H, s), 6.43 (1H, d, J=3Hz), 6.62
(2H, s), 6.66 (1H, d, J=1.5Hz), 7.10 (1H, d,
J=1.5Hz), 7.15-7.38 (10H, m), 7.53 (1H, s),
7.77 (1H, d, J=8.5Hz), 7.84 (1H, d, J=1.5Hz),
20 9.57 (1H, d, J=4Hz).

Compound of Example 28

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

1.7-1.9 (2H, m), 2.89 (2H, t, J=8Hz), 3.07 (2H, t, J=7.5Hz), 3.2-3.4 (4H, m), 5.99 (2H, s), 6.0-6.1 (1H, m), 6.47 (1H, d, J=8.5Hz), 6.7-6.8 (1H, m), 6.8-6.9 (1H, m), 7.2-7.5 (7H, m), 7.57 (1H, s), 7.8-7.9 (2H, m), 8.0-8.1 (1H, m)

Compound of Example 31

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.25-2.4 (2H, m), 2.9-3.1 (2H, m), 3.5-3.65 (2H, m), 4.1-4.3 (4H, m), 5.97 (2H, s), 7.02 (1H, t, J=7.5Hz), 7.11-7.43 (9H, m), 7.60-7.64 (2H, m), 7.71-7.75 (2H, m), 7.81 (1H, d, J=1.5Hz), 9.09 (1H, s), 9.25 (1H, t, J=8Hz).

15 Compound of Example 35

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.2-2.35 (2H, m), 3.4-3.5 (2H, m), 4.3-4.4 (2H, m), 6.05 (2H, s), 6.5-6.6 (1H, m), 7.1-7.2 (1H, m), 7.2-7.5 (9H, m), 7.7-7.8 (1H, m), 8.1-8.2 (1H, m), 9.62 (1H, s).

Compound of Example 36

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.26 (2H, m), 3.75 (2H, t, J=7Hz), 4.2 (2H, t, J=7Hz), 6.06 (2H, s), 6.48 (1H, d, J=3Hz), 7.24-7.5 (10H, m),

7.7-7.86 (5H, m), 8.07 (1H, s), 9.60 (1H, s).

Compound of Example 37

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.26 (3H, t, J=7Hz), 4.15-4.3 (2H, m),
5 4.84 (2H, s), 6.06 (2H, s), 6.56 (1H, d, J=3Hz),
7.12 (1H, d, J=3Hz), 7.23-7.47 (7H, m), 7.75
(1H, d, J=8.5Hz), 8.12 (1H, s), 9.62 (1H, s).

Compound of Example 38

¹H-NMR (250MHz, CDCl₃) δ ppm:

10 1.95-2.1 (2H, m), 2.92 (2H, t, J=8.5Hz),
3.13 (2H, t, J=7Hz), 3.36 (2H, t, J=8Hz), 3.83
(2H, t, J=7.5Hz), 6.02 (2H, s), 6.44 (1H, d,
J=8.5Hz), 7.25-7.33 (7H, m), 7.39 (1H, d,
J=1.5 Hz), 7.52 (1H, s), 7.69-7.73 (3H, m),
15 7.82-7.85 (2H, m), 9.40 (1H, s).

Compound of Example 39

¹H-NMR (250MHz, CDCl₃) δ ppm:

2.2-2.3 (2H, m), 3.10 (2H, t, J=7Hz),
3.44 (2H, t, J=6Hz), 3.75-3.85 (2H, m),
20 4.30 (2H, t, J=6Hz), 5.97 (2H, s), 7.03 (1H, s),
7.12-7.37 (10H, m), 7.61-7.66 (2H, m),
7.8-7.9 (1H, m).

Compound of Example 40

¹H-NMR (250MHz, CDCl₃) δ ppm:

- 1.31 (2H, brs), 1.70-1.81 (2H, m),
2.83 (2H, t, J=7Hz), 2.97 (2H, t, J=8Hz),
5 3.12 (2H, t, J=7.5Hz), 3.36 (2H, t, J=8Hz),
6.02 (2H, s), 6.45 (1H, d, J=8.5Hz), 7.23-7.32
(7H, m), 7.38 (1H, d, J=2Hz), 7.53 (1H, s),
7.71 (1H, d, J=9Hz), 9.43 (1H, s).

Compound of Example 41

- 10 ¹H-NMR (250MHz, DMSO-d₆) δ ppm:

2.44 (2H, t, J=7Hz), 2.87 (2H, t, J=7Hz),
5.99 (2H, s), 6.83 (1H, d, J=9Hz), 7.21-7.40
(6H, m), 7.57-7.6 (1H, m), 7.72 (1H, s),
7.86-7.88 (2H, m), 10.08 (1H, s).

- 15 Compound of Example 46

¹H-NMR (250MHz, DMSO-d₆) δ ppm

6.01 (2H, s), 6.50 (1H, d, J=9.5Hz),
7.22-7.41 (7H, m), 7.84-7.93 (4H, m),
8.25 (1H, s).

- 20 Compound of Example 49

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

1.9-2.1 (2H, m), 2.5-2.6 (2H, m), 2.8-3.0 (2H, m),
3.6-3.8 (2H, m), 3.9-4.1 (2H, m), 5.99 (2H, s),
7.1-7.5 (7H, m), 7.6-8.0 (4H, m).

Compound of Example 50

¹H-NMR (250MHz, CDCl₃) δ ppm:

1.9-2.1 (2H, m), 3.28-3.34 (4H, m),
3.77 (2H, t, J=7Hz), 4.26 (2H, t, J=4Hz),
5 6.01 (2H, s), 6.63 (1H, d, J=9Hz),
7.11-7.40 (9H, m), 7.70-7.74 (3H, m),
7.81-7.87 (2H, m), 9.34 (1H, s).

Example 51

To 0.66 g of 1-benzyl-6-chloro-2-(indol-5-ylaminocarbonyl)benzimidazole was added 50 ml of
10 dimethylformamide, further added 170 mg of oily sodium
hydride, said mixture was stirred under nitrogen gas
atmosphere at 60°C for 1 hour. Under cooling at 0°C,
0.14 ml of allyl bromide was added to the reaction
15 mixture, and stirred at room temperature overnight,
then water was added thereto and extracted with ethyl
acetate, the extract was washed with water and an
aqueous solution saturated with sodium chloride. The
washed extract was dried with anhydrous magnesium
20 sulfate, and the solvent was removed by distillation
under reduced pressure. The residue thus obtained was
subjected to a silica gel column chromatography
(eluent: 10% n-hexane/dichloromethane), recrystallized
from ethyl acetate-ethanol, there was obtained 0.35 g
25 of 1-benzyl-6-chloro-2-(1-allylindol-5-ylamino-
carbonyl)benzimidazole as in the form of colorless
needle crystals.

Melting point: 154-155°C.

By using suitable starting materials and by a method similar to that of employed in Example 51, there were obtained compounds of the above-mentioned Examples
5 3, 4, 6-8, 10-20, 22-29, 31, 33-40, 42-45 and 47-50.

Example 52

To 3.8 g of 1-benzyl-6-chloro-2-[1-(3-chloro-propyl)indol-5-ylaminocarbonyl]benzimidazole was added 100 mg of dimethylformamide, further added 1.4 g of
10 1H-1,2,3,4-tetrazol, 2.2 g of potassium carbonate and 7.2 g of sodium iodide, the mixture was heated and stirred at 100°C for 2 days. Water was added to the reaction mixture, and extracted with ethyl acetate, the extract was washed with water and an aqueous solution
15 saturated with sodium chloride. The washed extract was dried with anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue thus obtained was subjected to a silica gel column chromatography (eluent: ethyl acetate/n-hexane=
20 1/1), after separation of isomers, there were obtained 1.1 g of 1-benzyl-6-chloro-2-{1-[3-(1,2,3,4-tetrazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole (A) as in form of colorless needle crystals by recrystallization from ethyl acetate-n-hexane, and 0.9 g of
25 1-benzyl-6-chloro-2-{1-[3-(1,2,3,4-tetrazol-2-yl)-propyl]indol-5-ylaminocarbonyl}benzimidazole (B) as in the form of pale yellow needle crystals by

recrystallization from dichloromethane-n-hexane.

Melting point of (A): 178-179°C

Melting point of (B): 146-147°C

By using suitable starting materials, and by
5 a method similar to that of employed in Example 52,
there were obtained compounds of the above-mentioned
Examples 3, 4, 6-8, 10-12, 17-20, 23-29, 31, 33, 34,
36, 38, 40, 43, 44, 47, 48 and 50.

Example 53

10 To 5 g of 1-benzyl-6-chloro-2-[1-(3-
phthalimidopropyl)indol-5-ylaminocarbonyl]benzimidazole
was added 100 ml of ethanol and stirred, then 0.5 ml of
hydrazine hydrate was added thereto, the mixture was
refluxed overnight. After cooled the reaction mixture
15 to room temperature, then white crystals were removed
by filtration. Water was added to the filtrate, and
made alkaline with 10% aqueous solution of potassium
hydroxide. This mixture was extracted with dichloro-
methane, the extract was washed with water, an aqueous
20 solution saturated with sodium chloride then was dried
with anhydrous magnesium sulfate. The solvent was
removed by distillation under reduced pressure. The
residue thus obtained was crystallized from ethyl
acetate-n-hexane, there was obtained 3.2 g of 1-benzyl-
25 6-chloro-2-[1-(3-aminopropyl)indol-5-ylaminocarbonyl]-
benzimidazole as in the form of yellow granular

crystals. Melting point: 106-108°C.

By using a suitable starting material, and a method similar to that of employed in Example 53, there was obtained compound of the above-mentioned Example 5 40.

Example 54

To 0.29 g of nicotinic acid was added 50 ml of dimethylformamide, further 1.2 g of 1-benzyl-6-chloro-2-[1-(3-aminopropyl)indol-5-ylaminocarbonyl]-
10 benzimidazole and 0.7 ml of triethylamine were added, the mixture was stirred under cooling at 0°C. Next, 0.49 g of diethylcyanophosphonate was dissolved in 20 ml of dimethylformamide and added thereto and the reaction mixture was stirred at room temperature for 1
15 day. After the reaction was finished, water was added then the whole mixture was extracted with ethyl acetate, the extract thus obtained was washed with water and an aqueous solution saturated with sodium chloride. The washed extract was dried with anhydrous
20 magnesium sulfate, then the solvent was removed by distillation under reduced pressure. The resulting residue was subjected to a silica gel column chromatography (eluent: 2% methanol/dichloromethane), recrystallized from chloroform, there was obtained 1 g
25 of 1-benzyl-6-chloro-2-{1-[3-(pyridin-3-ylcarbonyl-amino)propyl]indol-5-ylaminocarbonyl}benzimidazole as in the form of yellow needle crystals.

Melting point: 206-207°C.

By using suitable starting materials and a method similar to that of employed in example 54, there were obtained compounds of the above-mentioned Examples 5 9, 12, 28, 33, 34 and 47.

Example 55

To 0.35 g of 1-benzyl-6-chloro-2-(3,4-dihydro-2(1H)-quinolinon-6-ylaminocarbonyl)-benzimidazole was added 30 ml of dioxane and 280 mg of 10 2,3-dichloro-5,6-dicyanobenzoquinone, and the reaction mixture was refluxed by heating. Over confirming the proceeding of reaction by means of a thin layer chromatography, 2,3-dichloro-5,6-dicyanobenzoquinone in small quantity was further added and refluxed by 15 heating for 1 day. The crystals being separated were collected by filtration, and recrystallized from chloroform-isopropyl alcohol, there was obtained 1-benzyl-6-chloro-2-[2(1H)-quinolinon-6-ylamino-caronyl]benzimidazole as in the form of pale brown 20 powdery product.

Melting point: higher than 290°C.

¹H-NMR (250MHz, DMSO-d₆) δ ppm:

6.01 (2H, s), 6.50 (1H, d, J=9.5Hz),

7.22-7.41 (7H, m), 7.84-7.93 (4H, m),

25 8.25 (1H, s).

Example 56

A mixture of 27.9 g of ethyl 1-benzyl-6-chlorobenzimidazol-2-carboxylate, 17.8 g of 1-[3-(imidazol-1-yl)propyl]-5-aminoindole, 8 g of sodium methy-
5 late and 600 ml of toluene was stirred at 100°C for 1.5 hours. The reaction mixture was cooled to room temperature, the crystals being separated were collected by filtration and washed with toluene. Thus obtained crystals were dissolved in 500 ml of chloro-
10 form, then 100 ml of water was added and the mixture was filtrated with Celite. The chloroform layer was taken by separation, after washed with water, the chloroform portion layer was dried with anhydrous magnesium sulfate, and the solvent was removed by
15 distillation to obtain brown oily product. This oily product was dissolved in methanol, further added n-hexane and the crystals being separated were collected by filtration, recrystallized from methanol and dried. There was obtained 31.8 g of 1-benzyl-6-
20 chloro-2-{1-[3-(imidazol-1-yl)propyl]indol-5-ylamino-carbonyl}benzimidazole.

Pale yellow needle crystals.

Melting point: 187-188°C.

25 By using suitable starting materials, and by a method similar to that of employed in Example 56, there were obtained compounds of the above-mentioned Examples 2 and 4-50.

Pharmacological tests

(1) Measurement of the activity for inhibiting cGMP PDE

Separation and partial purification of PDE (phosphodiesterase) from human platelets, and measurement of the activity for inhibiting cGMP PDE were conducted by the method of Hidaka, et al. [Biochimica et Biophysica Acta, Vol. 429, (1976), pp. 485-497]. The platelets obtained from human healthy adult were washed, and suspended in TRIS-buffer solution, then said suspension was treated by centrifugal separation, the supernatant was subjected to a DEAE-cellulose treatment and fractionated into FI to FIII fractions by a method of concentration gradient of sodium acetate. Thus obtained FI fraction was used as the sample of cGMP-PDE. The activity for inhibiting cGMP-PDE was measured by using 0.4 μ M of [3 H]-cGMP.

The results are shown in Table 34 as follows.

Table 34

| | | Activity for inhibiting | |
|--------------------------|------------|--|--|
| <u>Test compound of:</u> | | <u>cGMP-PDE [IC₅₀ (μM)]</u> | |
| 5 | Example 2 | 0.02 | |
| | Example 3 | 0.01 | |
| | Example 4 | 0.06 | |
| | Example 9 | 0.08 | |
| | Example 11 | 0.01 | |
| 10 | Example 20 | 0.01 | |
| | Example 21 | 0.02 | |
| | Example 25 | 0.12 | |
| | Example 28 | < 0.01 | |
| | Example 31 | 0.03 | |
| 15 | Example 32 | 0.06 | |
| | Example 33 | < 0.01 | |
| | Example 41 | 0.02 | |
| | Example 42 | 0.1 | |
| | Example 44 | 0.014 | |
| 20 | Example 46 | < 0.01 | |
| | Example 47 | < 0.01 | |

(2) Measurement of the activity for inhibiting
proliferation of rat A10 cells

Test was conducted by the modified method of
N. Morisaki [Atherosclerosis, Vol. 71, (1988), pp.
25 165-171]. The rat A10 cells (purchased from Dainippon
Pharmaceutical Co., Ltd.) were inoculated on a 24 wells
immunoplate at a density of 10,000 cells/well, and were

cultured in 10% FBS (fetal bovine serum) for 2 days, and in order to introduce the cells into the resting stage, the cells were further cultured in a serum-free medium for 2 days. After that, 1% FBS was added thereto for stimulating the proliferation, of the cells and at the same time, a test compound and 0.5 μ Ci/well of [3 H]-thymidine were added. As to the index of synthesized amount of DNA, the quantity of [3 H]-thymidine being uptaken by the cells was measured at the time of 24 hours after the final cultivation was started.

The results are shown in Table 35 as follows.

Table 35

| 15 | Test compound of: | Activity for inhibiting proliferation of rat A10 cells |
|----|-------------------|--|
| | | <u>[IC₅₀ (μM)]</u> |
| | Example 2 | 0.4 |
| | Example 3 | 0.5 |
| 20 | Example 4 | 0.3 |
| | Example 6 | 0.66 |
| | Example 7 | 0.49 |
| | Example 11 | 0.97 |
| | Example 12 | 0.69 |
| 25 | Example 18 | 0.48 |
| | Example 20 | 0.85 |
| | Example 32 | 0.24 |
| | Example 33 | 1.27 |
| | Example 42 | 0.95 |
| 30 | Example 47 | 0.67 |

(3) Measurement of the activity for inhibiting
proliferation of the human fibroblast

Similar to the activity for inhibiting
proliferation of rat A10 cells as mentioned above, the
5 activity for inhibiting proliferation of the human
fibroblast (purchased from Dainippon Pharmaceutical
Co., Ltd.) was determined by measuring the uptake
amount of [³H]-thymidine. Compounds of Examples 3, 16,
31, 33, 45 and 47 were used for the test, and the
10 measured values of IC₅₀ were, 0.04 μM, 0.049 μM, 0.18
μM, 0.042 μM, 0.041 μM and 0.021 μM, respectively.

(4) Measurement of the activity for inhibiting
proliferation of the T cells

Test was conducted by the method as disclosed
15 in "Current Protocol in Immunology" [Edited by Coligan,
et al., (1991)] Chapter 3, page 12 (Published from
Willy Interscience, Inc.). After sacrificed a Balb/c
strain male mouse, the spleen was enucleated and a
suspension of the spleen cells in RPMI-1640 culture
20 medium was prepared. Said suspension was filtered
through a nylon fiber mesh, and subjected to a
centrifugal separation (1,200 rpm, for 5 minutes),
there were added on pellet 5 ml of 0.15 M ammonium
chloride, 10 mM potassium hydrogencarbonate, and 0.1 mM
25 disodium salt of EDTA (pH 7.2) per one spleen so
as to suspend the cells, and the suspension was
incubated at 37°C for 5 minutes. A suitable amount of

RPMT-1640 culture medium was added to the suspension, and this mixture was subjected to a centrifugal separation (1,200 rpm, for 5 minutes), the separated cells were washed, after repeated further washing operations
5 twice, the cells were resuspended in RPMI-1640 culture medium containing 10% FBS (RPMI-10). After counted the number of cells by using a hemacytometer, a suspension containing cell density of $10^6/\text{ml}$ was prepared by diluting with RPMI-10 culture medium. A test compound
10 was dissolved in dimethyl sulfoxide to prepare a solution of 2×10^{-2} M, then prepared 6 stages of 10-fold dilution sequences. Each one of these 10-fold dilution sequences was placed on a 96-well tissue culture plate in an amount of 10 $\mu\text{l}/\text{well}$ (the final concentrations of
15 test compounds: 10^{-9} to 10^{-4} M), and added the previously prepared cell suspension in an amount of 190 $\mu\text{l}/\text{well}$. There was added 40 $\mu\text{g}/\text{ml}$ of Concanavaline A in an amount of 10 $\mu\text{l}/\text{well}$, and incubated at 37° for 2 days, under 5% carbon dioxide gas phase.

20 20 $\mu\text{Ci}/\text{ml}$ of [methyl- ^3H] thymidine was added in an amount of 10 $\mu\text{l}/\text{well}$, after further incubated overnight, by using a cell harvester the cells were recovered on the filter of the harvester. The filter was cut out from the cell harvester and put in a vial,
25 then 5 ml of a scintillation cocktail (ACS-II) was added, and measured by using a liquid scintillation counter. By using the compound of Example 3 as test compound, IC_{50} value was 2 μM .

(5) Determination of the activity for inhibiting
chronic contactive dermatitis

The activity for inhibiting chronic
contactive dermatitis [J. Dermatol. Sci., Vol. 8,
5 (1994), page 54] which is analogous to atopic
dermatitis being reported by Kitagaki, et al. was
discussed by using the method as follows. The
right-side ear pinna of Balb/c strain male mouse was
subjected to antigen sensitization by coating with 20
10 μ l of acetone solution of 1% trinitrochlorobenzene
(TNCB). 7 Days after the antigen sensitization, the
same right-side pinna was subjected to antigen
induction by coating with 20 μ l of 1% TNCB acetone
solution. The treatment of antigen induction was
15 repeated in every 2 days so as to induced chronic
contactive dermatitis. In this test, increase of
thickness of the right-side ear pinna was induced by
passing into a chronic state of the contactive
dermatitis. The test compound was dissolved in
20 acetone-methanol (4:1 by v/v) and 20 μ l of this
solution was administered by coating on the right-side
of ear pinna once a day from 24th day after the antigen
induction for 2 weeks. As to the control, the only
the solvent was similarly administered. The antigen
25 induction by the test compound during administration
period was conducted at 30 minutes before the
administration. The thickness of the ear pinna of 14th
day after the administration was measured by a dial

thickness gauge.

The results are shown in Table 36 as follows.

Table 36

| Concentration (%) of compound of Example 3 | Thickness of ear pinna ($\times 10 \mu\text{m}$) | Inhibition rate (%) |
|--|--|---------------------------|
| 0 (Control) | 137.1 ± 6.2 | - |
| 0.1 | 120.4 ± 5.3 | 12 |
| 0.3 | 105.0 ± 7.2 | 23 * |
| 1.0 | 64.5 ± 1.6 | 53 * |

* Significant difference between the control:
 $p < 0.01$ Dunnett's test

Number of the test animals: 8

(6) Determination of the activity for inhibiting
TPA induced inflammation

5 Test was conducted by the modified method of
Carlson, et al. [Agents Actions, Vol. 26, (1989),
page 319]. Thus, to the ear pinna of ICR strain female
mouse, 20 μl of acetone solution of 12-O-tetradecanoyl-
phorbol-13-acetate (TPA) in the concentration of 200
10 $\mu\text{g}/\text{ml}$ was coated to induce inflammation. The thickness
of ear pinna of 4 hours after the TPA coating was
measured, and difference of the last value was defined
as the ear pinna inflammation. Test compound was
dissolved in acetone-methanol (4:1 by v/v) to make the

concentration of 1%. 20 μ l of test compound solution was coated on the ear pinna 30 minutes before the TPA coating. By using compound of Example 3 as test compound, the inflammation was inhibited at the rate of 66%.

(7) Determination of the activity for inhibiting proliferation of rat mesangial cells

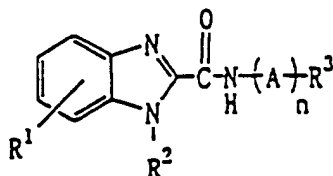
In accordance with the method of F. Jaffer, et al. [Am. J. Pathol., Vol. 135, (1989), pages 261-269], the mesangial cells were collected. Under anesthetized condition, the kidney of a rat was aseptically enucleated and the medulla renis was cut out, then the cortex renis was pressed to a sieve (120 mesh) made of stainless steel. The fraction of cortex renis passed through the sieve was put on another sieve of 200 mesh and washed with PBS (phosphate-buffered saline), the fraction being remained on the sieve was confirmed as the glomerulus. This fraction was cultured in RPMI 1640 medium [containing 15% of fetal calf serum (FCS), and 5 μ g/ml of insulin] for 4 weeks. This fraction was further subcultured twice, and the remaining cells were thought of as the mesangial cells for use of this experiment.

Determination of the activity for inhibiting proliferation of rat mesangial cells was conducted in accordance with the method of M. B. Ganz, et al. [Am. J. Physiol., Vol. 259, (1990), pages F269-F278].

Thus 2×10^4 /ml of mesangial cells were inoculated on a culture plate (48 wells, each well having the capacity of 0.5 ml), and cultured with RPMI medium (containing 15% FCS) for 3 days. The RPMI
5 medium was then changed to another RPMI medium wherein the concentration of FCS was decreased to 0.5%, and further cultured for 3 days. Next, the RPMI medium was changed to another RPMI medium containing the same concentration of FCS, and added the test compound being
10 dissolved in dimethyl sulfoxide (the final concentration of dimethyl sulfoxide was lower than 0.1%) and 5 ng/ml (the final concentration) of platelet-derived growth factor BB (PDGF-BB). After 24 hours, 1 μ Ci/well of [3 H]-thymidine was added, and incubated for
15 additional 24 hours. The supernatant of the culture medium was taken up, and the amount of [3 H]-thymidine up-taken into the cells was measured by use of scintillation counter. IC_{50} value measured by using compound of Example 3 for the test was 0.79 μ M.

CLAIMS

1. Benzimidazole derivatives or salts thereof represented by the general formula,



wherein R^1 is a hydrogen atom or a halogen atom;

5 R^2 is a phenyl-lower alkyl group;

R^3 is a heterocyclic group selected from the group consisting of an indolyl group, indolinyl group, 1H-indazolyl group, 2(1H)-quinolinonyl group, 3,4-dihydro-2(1H)-quinolinonyl group and 3,4-dihydro-1,4(2H)-benzoxazinyl group, said heterocyclic group may have 1 to 3 substituents selected from the group consisting of:

a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and

oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group;

A is a lower alkylene group; and

n is 0 or 1.

2. The benzimidazole derivatives or salts thereof according to Claim 1, wherein R^3 is an indolyl group, said indolyl group may have 1 to 3 substituents selected from the group consisting of:
a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring,

having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group.

3. The benzimidazole derivatives or salts thereof according to Claim 1, wherein R^3 is an indolinyl group, said indolinyl group may have 1 to 3 substituents selected from the group consisting of:

a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group.

4. The benzimidazole derivatives or salts

thereof according to Claim 1, wherein R^3 is a 1H-indazolyl group, said 1H-indazolyl group may have 1 to 3 substituents selected from the group consisting of a group of:

- 5 a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur
- 10 atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a
- 15 lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the
- 20 substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group
- 25 may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxy carbonyl group; a phenoxy-lower alkyl group which may have cyano group

as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxy-carbonyl-substituted lower alkyl group.

5. The benzimidazole derivatives or salts thereof according to Claim 1, wherein R^3 is a 2(1H)-quinolinonyl group or 3,4-dihydro-2(1H)-quinolinonyl group, said 2(1H)-quinolinonyl group or 3,4-dihydro-2(1H)-quinolinonyl group may have 1 to 3 substituents selected from the group consisting of a group of:

10 a group of the formula $-B-R^4$, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a

20 lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the

25 substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other

nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group));
a lower alkenyl group; a lower alkoxycarbonyl group;
5 a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group.

6. The benzimidazole derivatives or salts
10 thereof according to Claim 1, wherein R^3 is a 3,4-dihydro-1,4(2H)-benzoxazinyl group, said 3,4-dihydro-1,4(2H)-benzoxazinyl group may have 1 to 3 substituents selected from the group consisting of:
a group of the formula $-B-R^4$, (B is a lower alkylene
15 group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen
20 atom, a lower alkyl group, a lower alkoxy group and oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-
25 carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the

substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group.

7. The benzimidazole derivatives or salts thereof according to Claim 2, wherein R^1 is a hydrogen atom; and n is 0.

8. The benzimidazole derivatives or salts thereof according to Claim 2, wherein R^1 is a hydrogen atom; and n is 1.

9. The benzimidazole derivatives or salts thereof according to Claim 2, wherein R^1 is a halogen atom; and n is 0.

10. The benzimidazole derivatives or salts thereof according to Claim 2, wherein R^1 is a halogen atom; and n is 1.

11. The benzimidazole derivatives or salts thereof according to Claim 3, wherein R^1 is a hydrogen atom; and n is 0.

12. The benzimidazole derivatives or salts

thereof according to Claim 3, wherein R^1 is a hydrogen atom; and \underline{n} is 1.

13. The benzimidazole derivatives or salts thereof according to Claim 3, wherein R^1 is a halogen atom; and \underline{n} is 0.

14. The benzimidazole derivatives or salts thereof according to Claim 3, wherein R^1 is a halogen atom; and \underline{n} is 1.

15. The benzimidazole derivatives or salts thereof according to Claim 4, wherein R^1 is a hydrogen atom; and \underline{n} is 0.

16. The benzimidazole derivatives or salts thereof according to Claim 4, wherein R^1 is a hydrogen atom; and \underline{n} is 1.

17. The benzimidazole derivatives or salts thereof according to Claim 4, wherein R^1 is a halogen atom; and \underline{n} is 0.

18. The benzimidazole derivatives or salts thereof according to Claim 4, wherein R^1 is a halogen atom; and \underline{n} is 1.

19. The benzimidazole derivatives or salts thereof according to Claim 5, wherein R^1 is a hydrogen atom; and \underline{n} is 0.

20. The benzimidazole derivatives or salts thereof according to Claim 5, wherein R^1 is a hydrogen atom; and \underline{n} is 1.

21. The benzimidazole derivatives or salts thereof according to Claim 5, wherein R^1 is a halogen

atom; and n is 0.

22. The benzimidazole derivatives or salts thereof according to Claim 5, wherein R¹ is a halogen atom; and n is 1.

5 23. The benzimidazole derivatives or salts thereof according to Claim 6, wherein R¹ is a hydrogen atom; and n is 0.

24. The benzimidazole derivatives or salts thereof according to Claim 6, wherein R¹ is a hydrogen atom; and n is 1.

25. The benzimidazole derivatives or salts thereof according to Claim 6, wherein R¹ is a halogen atom; and n is 0.

26. The benzimidazole derivatives or salts thereof according to Claim 6, wherein R¹ is a halogen atom; and n is 1.

27. The benzimidazole derivatives or salts thereof according to Claims 7 to 26, wherein a 5- to 11-membered saturated or unsaturated single ring or binary ring heterocyclic group represented by the group of R⁴ is a pyrrolidinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, pyridyl, homopiperazinyl, 1,2,5,6-tetrahydropyridyl, thienyl, quinolinyl, 1,4-dihydroquinolinyl, benzothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, carbostyryl, 3,4-dihydrocarbostyryl, 1,2,3,4-tetrahydroquinolinyl, indolyl, isoindolyl, indolinyl, benzimidazolyl, benzoxazolyl, imidazolidinyl, isoquinolinyl,

quinazolidinyl, 1,2,3,4-tetrahydroisoquinolinyl,
1,2-dihydroisoquinolinyl, quinoxalinyl, cinnolinyl,
phthalazinyl, 1,2,3,4-tetrazolyl, 1,2,4-triazolyl,
chromanyl, isoindolinyl, isochromanyl, pyrazolyl,
5 imidazolyl, pyrazolidinyl, imidazo[1,2-a]pyridyl,
benzofuryl, 2,3-dihydrobenzo[b]furyl, benzothienyl,
1-azacycloheptyl, 4H-chromenyl, 1H-indazolyl, 2-
imidazolinyl, 2-pyrrolinyl, furyl, oxazolyl, oxazol-
idinyl, isoxazolyl, thiazolyl, isothiazolyl, pyranyl,
10 pyrazolidinyl, 2-pyrazolinyl, quinuclidinyl, 1,4-
benzoxazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-
dihydro-2H-1,4-benzothiazinyl, 1,4-benzothiazinyl,
1,2,3,4-tetrahydroquinoxalinyl, 1,3-dithia-2,4-
dihydronaphthalenyl, tetrahydro-1,3-oxazinyl,
15 tetrahydroxazolyl or 1,4-dithianaphthalenyl group.

28. The benzimidazole derivatives or salts thereof
according to Claims 7 to 26, wherein the heterocyclic
group represented by the group of R^4 is an imidazolyl
group, pyrazolyl group or 1,2,4-triazolyl group.

20 29. The benzimidazole derivatives or salts
thereof according to Claims 7 to 26, wherein R^4 is
a group of the formula $-NR^5R^6$ (wherein R^5 and R^6 are
the same as defined in Claim 1).

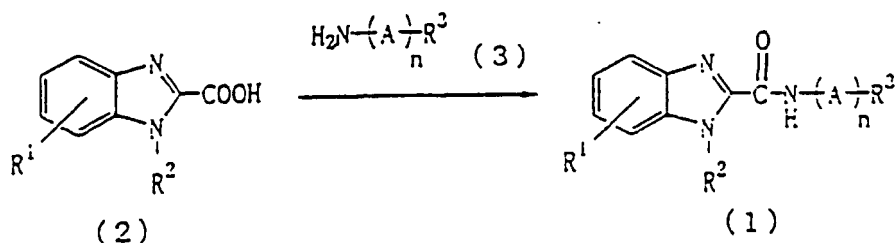
30. 1-Benzyl-6-chloro-2-{1-[3-(imidazol-1-
25 yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

31. 1-Benzyl-6-chloro-2-{1-[3-(N-cyclohexyl-N-
methylamino)propyl]indol-5-ylaminocarbonyl}-
benzimidazole.

32. 1-Benzyl-6-chloro-2-{1-[3-(pyrazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.
33. 1-Benzyl-6-chloro-2-{1-[3-(1,2,4-triazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.
- 5 34. 1-Benzyl-6-chloro-2-{1-[3-(3,5-dimethylisoxazol-4-ylcarbonylamino)propyl]indol-5-ylaminocarbonyl}benzimidazole.
35. 1-Benzyl-6-chloro-2-{1-[3-(4-phenyl-4-hydroxypiperidin-1-yl)propyl]indol-5-ylaminocarbonyl}-
10 benzimidazole.
36. 1-Benzyl-6-chloro-2-{4-[3-(pyridin-2-ylcarbonylamino)propyl]-3,4-dihydro-1,4(2H)-benzoxazin-7-ylaminocarbonyl}benzimidazole.
37. A pharmaceutical composition for inhibiting
15 the enzymatic activity of cGMP PDE characterized by containing, as the active ingredient, the benzimidazole derivative or salt thereof as claimed in Claim 1.
38. A pharmaceutical composition for inhibiting proliferation of the cells characterized by containing,
20 as the active ingredient, a benzimidazole derivative or salt thereof as claimed in Claim 1.
39. A pharmaceutical composition for inhibiting synthesis and secretion of collagen characterized by containing, as the active ingredient, the benzimidazole
25 derivative or salt thereof as claimed in Claim 1.
40. An immunosuppressive agent characterized by containing, as the active ingredient, the benzimidazole derivative or salt thereof as claimed in Claim 1.

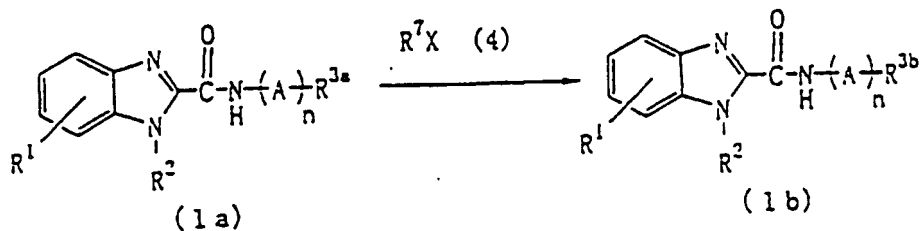
41. An antiinflammatory agent characterized by containing, as the active ingredient, the benzimidazole derivative or salt thereof as claimed in Claim 1.

42. A process for preparing a benzimidazole derivative of the general formula (1), by reacting a benzimidazole compound of the formula (2) with an amine of the formula (3),



wherein R^1 , R^2 , R^3 , A and n are the same as defined in Claim 1.

43. A process for preparing a benzimidazole derivative of the general formula (1b), by reacting a compound of the formula (1a) with a compound of the formula (4),



wherein R^1 , R^2 , A and n are the same as defined above;
 and R^{3a} is a heterocyclic group as defined in R^3 , which

may have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group, further R^{3a} is a heterocyclic group as defined in R^3 , having a group of the formula $-NH-$ in said heterocyclic group:

R^{3b} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

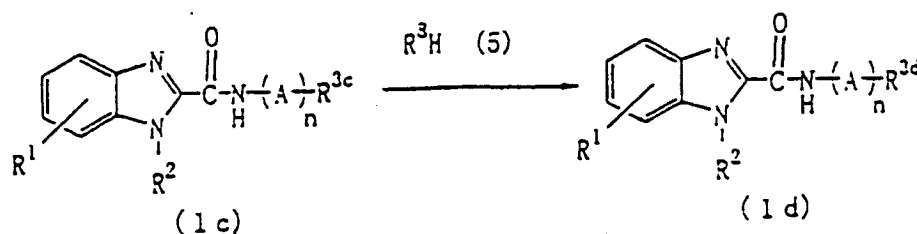
a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group; further R^{3b} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^7)-$ (R^7 is a group of the formula $-B-R^4$ (wherein B and R^4 are the same as defined above); a lower alkenyl group, a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituent in the phenyl ring; a halogen substituted-lower alkyl group; or

a lower alkoxycarbonyl substituted-lower alkyl group)
in said heterocyclic group;

R^7 is the same as defined above;

X is a halogen atom, a lower alkanesulfonyloxy group,
5 an arylsulfonyloxy group or an aralkylsulfonyloxy
group.

44. A process for preparing a benzimidazole
derivative of the formula (1d), by reacting a compound
of the formula (1c) with a compound of the formula (5),



10 wherein R^1 , R^2 , A and n are the same as defined above;
and R^{3c} is a heterocyclic group as defined in R^3 , which
may have 1 to 2 substituents selected from the group
consisting of:

a group of the formula $-B-R^4$ (B and R^4 are the same as
15 defined above); a lower alkenyl group; a lower alkoxy-
carbonyl group; a phenoxy-lower alkyl group which may
have cyano groups as the substituents in the phenyl
ring; a halogen substituted-lower alkyl group; and
a lower alkoxycarbonyl substituted-lower alkyl group;
20 further R^{3c} is a heterocyclic group as defined in R^3 ,

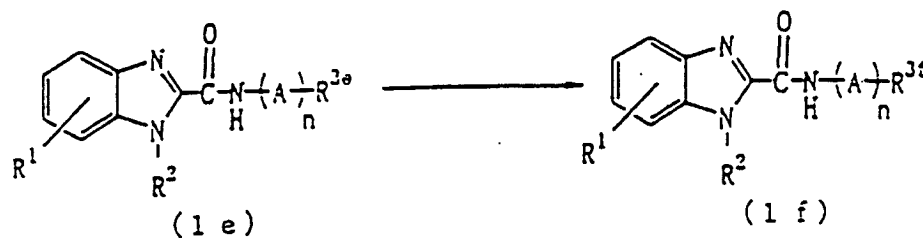
having a group of the formula $-N(R^9)-$ (R^9 is a halogen substituted-lower alkyl group) in said heterocyclic group;

R^{3d} is a heterocyclic group as defined in R^3 , which may
5 have 1 to 2 substituents selected from the group consisting of:

a group of the formula $-B-R^4$ (B and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may
10 have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a lower alkoxy-carbonyl substituted-lower alkyl group; further, R^{3d} is a heterocyclic group as defined in R^3 , having a group of the formula $-N(R^{10})-$ (R^{10} is a group
15 of the formula $-B-R^4$ (B and R^4 are the same as defined above); or a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring) in said heterocyclic group;

R^8 is a group of the formula $-R^{4a}$ (R^{4a} is a hetero-
20 cyclic group as defined in R^4 , having at least one group of the formula $-N<$ in said heterocyclic group, or a group of the formula $-NR^5R^6$ (R^5 and R^6 are the same as defined above); or a phenoxy group which may have cyano groups as the substituents in the phenyl ring.

25 45. A process for preparing a benzimidazole derivative of the formula (1f), by introducing a compound of the formula (1e) with hydrazine in a suitable solvent; or hydrolysis of a compound (1e),



wherein R^1 , R^2 , \underline{A} and \underline{n} are the same as defined above;
 and R^{3e} is a heterocyclic group as defined in R^3 , which
 may have 1 to 2 substituents selected from the group
 consisting of:

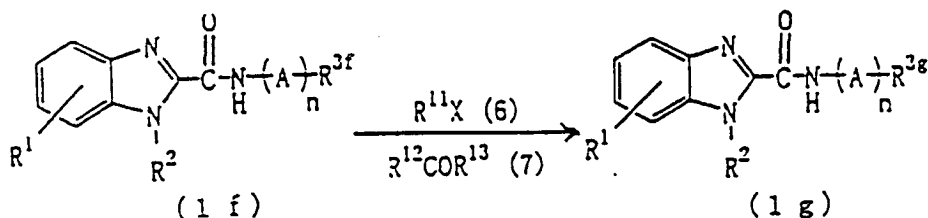
- 5 a group of the formula $-\underline{B}-R^4$ (\underline{B} and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a
- 10 lower alkoxy carbonyl substituted-lower alkyl group; further R^{3e} is a heterocyclic group as defined in R^3 , having a group of the formula $-\text{N}(\text{R}^{15})-$ (R^{15} is a phthalimide substituted-lower alkyl group) in said heterocyclic group;
- 15 R^{3f} is a heterocyclic group as defined in R^3 which may have 1 to 2 substituents selected from the group consisting of:
- a group of the formula $-\underline{B}-R^4$ (\underline{B} and R^4 are the same as defined above); a lower alkenyl group; a lower
- 20 alkoxy carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituent(s) in

the phenyl ring; a halogen substituted-lower alkyl group; and

a lower alkoxy carbonyl substituted-lower alkyl group; further R^{3f} is a heterocyclic group as defined in R^3 ,

5 having a group of the formula $-N(R^{16})-$ (R^{16} is an amino group-substituted lower alkyl group) in the heterocyclic ring.

46. A process for preparing a benzimidazole derivative of the formula (1g), by reacting a compound
10 of the formula (1f) with a compound of the formula (6); or with a compound of the formula (7),

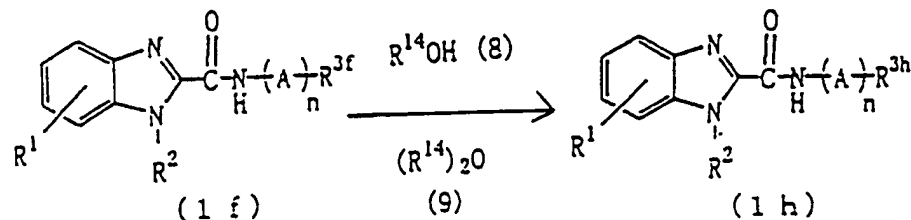


wherein R^1 , R^2 , \underline{A} , \underline{n} and R^{3f} are the same as defined above; and R^{3g} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the
15 group consisting of:

a group of the formula $-\underline{B}-R^4$ (\underline{B} and R^4 are the same defined above); a lower alkenyl group; a lower alkoxy carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl
20 ring; a halogen substituted-lower alkyl group; and a

lower alkoxycarbonyl substituted-lower alkyl group;
 further R^{3g} is a heterocyclic group as defined in R^3 ,
 having a group of the formula $-N(B-NR^{5a}R^{11})-$ (B is the
 same as defined above; R^{5a} is a hydrogen atom, a lower
 5 alkyl group, a cycloalkyl group, a pyridylcarbonyl
 group, an isoxazolyldcarbonyl group which may have 1 to
 3 lower alkyl groups as the substituents; a pyrrolyl-
 carbonyl group or an amino group substituted-lower
 alkyl group which may have lower alkyl groups as the
 10 substituents; R^{11} is a lower alkyl group, a cycloalkyl
 group or an amino group substituted-lower alkyl which
 may have lower alkyl groups as the substituents in said
 heterocyclic group; R^{11} is the same as defined above;
 R^{12} and R^{13} are each, a hydrogen atom or a lower alkyl
 15 group, respectively.

47. A process for preparing a benzimidazole
 derivative of the formula (1h), by reacting a compound
 of the formula (1f) with a compound of the formula (8);
 or with a compound of the formula (9),



wherein R^1 , R^2 , \underline{A} , \underline{n} and R^{3f} are the same as defined above; and R^{3h} is a heterocyclic group as defined in R^3 , which may have 1 to 2 substituents selected from the group consisting of:

- 5 a group of the formula $-\underline{B}-R^4$ (\underline{B} and R^4 are the same as defined above); a lower alkenyl group; a lower alkoxy-carbonyl group; a phenoxy-lower alkyl group which may have cyano groups as the substituents in the phenyl ring; a halogen substituted-lower alkyl group; and a
- 10 lower alkoxy-carbonyl substituted-lower alkyl group; further R^{3h} is a heterocyclic group as defined in R^3 , having a group of the formula $-\underline{N}(\underline{B}-NR^{5a}R^{14})-$ (\underline{B} and R^{5a} are the same as defined above; and R^{14} is a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may
- 15 have 1 to 3 lower alkyl groups as the substituents, or a pyrrolylcarbonyl group) in said heterocyclic group.

INTERNATIONAL SEARCH REPORT

Int. Nat. Application No.

PCT/JP 96/01841

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/12 A61K31/415 C07D401/12 C07D521/00 C07D403/14
C07D401/14 C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | CHEMICAL ABSTRACTS, vol. 120, no. 15, 11 April 1994 Columbus, Ohio, US; abstract no. 191719v, T. OKU ET AL.: "Preparation of benzylimidazoles as c-GMP phosphodiesterase inhibitors." page 1050; column 2; XP002015160 cited in the application see abstract & JP,A,05 222 000 (FUJISAWA PHARMACEUTICAL CO., LTD.) 31 August 1993 ----- | 1-38 |

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 October 1996

Date of mailing of the international search report

15.10.96

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